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THE AMERICAN REVIEW OF TUBERCULOSIS

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MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

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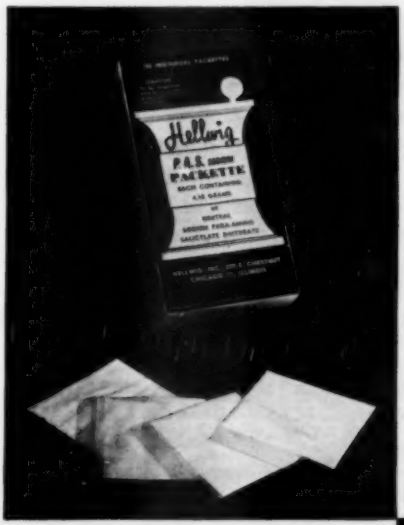

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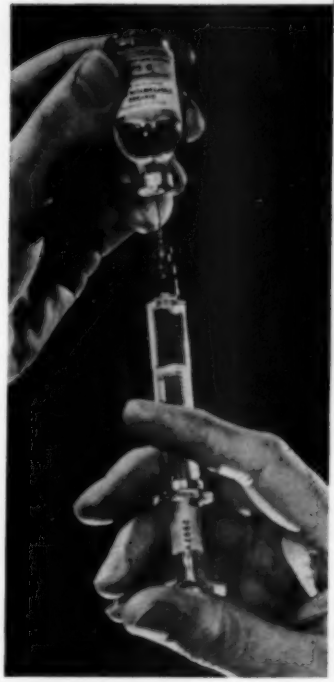

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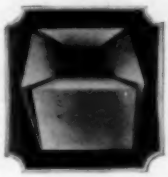

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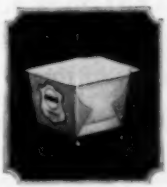

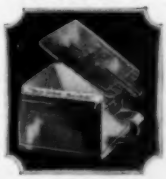

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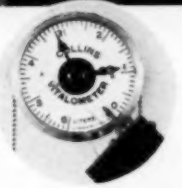

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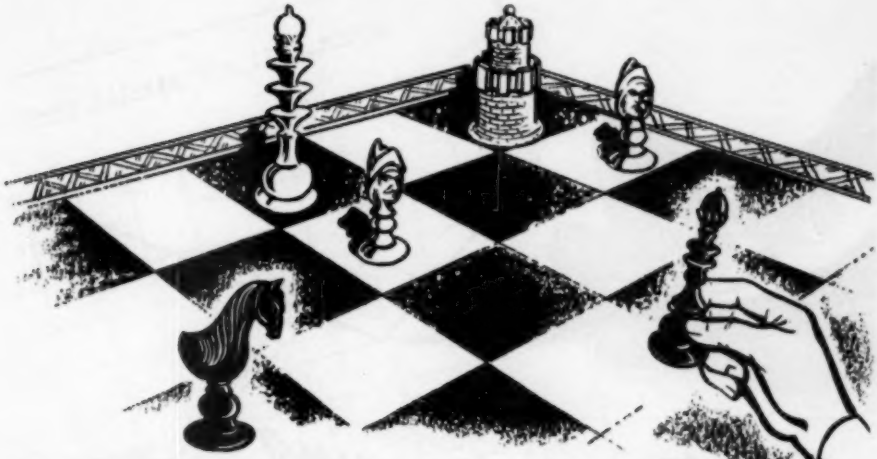

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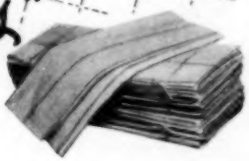

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ERRATUM

In Volume 63, No. 4, 1951, "An Evaluation of Media for Diagnostic Cultures of Tubercle Bacilli" a change in the formula for Dubos oleic acid-albumin-agar with penicillin (100 units per ml.) on page 460 should be made. Instead of

Ferric ammonium citrate....0.05 gm. (*1 ml.* of 1 per cent solution)
$CaCl_2$.....*0.005 gm.* (1 ml. of 0.05 per cent solution)

it should read:

Ferric ammonium citrate....0.05 gm. (*5 ml.* of 1 per cent solution)
$CaCl_2$.....*0.0005 gm.* (1 ml. of 0.05 per cent solution)

THE AMERICAN REVIEW
OF
TUBERCULOSIS

VOLUME 64 *September 1951* NUMBER 3

AN EVALUATION OF THE ROLE OF SERIAL CHEST ROENTGENOGRAMS IN ESTIMATING THE PROGRESS OF DISEASE IN PATIENTS WITH PULMONARY TUBERCULOSIS[1,2]

J. YERUSHALMY, L. H. GARLAND, J. T. HARKNESS, H. C. HINSHAW, E. R. MILLER, S. J. SHIPMAN, AND H. B. ZWERLING

(Received for publication April 2, 1951)

INTRODUCTION

The purpose of this study is to provide an evaluation of the reliability of the interpretation of serial roentgenograms of the chest. Such interpretations are among the most valuable criteria for assessing the course of disease in a patient with pulmonary tuberculosis. The major changes occurring in a pulmonary lesion are usually reflected in changes in its roentgenographic shadows. Serial roentgenograms have therefore long been accepted as an objective test of the "progress of the disease" and its "activity." Nevertheless, to our knowledge, the reliability of the interpretation of serial roentgenograms has not previously been put to an objective test.

The roentgenogram of the chest is essential for both "case finding" and "case management" in pulmonary tuberculosis. It fulfills its functions best when used as a *diagnostic aid*, that is, as an instrument for providing objective evidence of disease to be integrated with other clinical and laboratory data. In practice, however, it often appears that the information revealed by the roentgenogram is taken as the sole guide in diagnosis and treatment.

In roentgenographic surveys of the chest, the interpretation of the film is of necessity the decisive factor in selecting those patients in need of further study. In the initial stages of disposition, great reliance again is placed on the appearance of the roentgenogram because the majority of patients discovered in surveys exhibit no symptoms, and the clinical and laboratory findings are within normal limits in a large majority of them. Consequently, the course of action is

[1] From the Division of Biostatistics, School of Public Health, and the Divisions of Radiology and Medicine of the School of Medicine and the E. V. Cowell Memorial Hospital, University of California, at Berkeley and San Francisco; the Departments of Radiology and Medicine, Stanford University School of Medicine at San Francisco, and Alta Bates Hospital, Berkeley.

[2] Assistance for the study was provided by the Eastman Kodak Co., the General Electric X-Ray Corporation, and the Picker X-Ray Corporation.

often decided upon by the significance attached to the roentgenographic findings by the radiologist and chest specialist.

In the subsequent study of patients found by survey to have roentgenographic evidence of disease, as well as in the treatment of active disease, additional information becomes available which assists the clinician in the management of the patient. In general, the data which are of greatest significance to the clinician are those pertaining to *change of status*. The observation of pertinent clinical, laboratory, and roentgenographic changes, singly or in combination, provides the basis for effective treatment. The most reliable estimate of changes in extent and character of a lesion is provided by roentgenography and is perceived by a comparison of serial chest films. For this reason it is perhaps not surprising that roentgenographic interpretation has been accepted with a degree of confidence surpassing that which should be accorded to any single diagnostic test. It is not uncommon that the evaluation of changes in serial chest films is relied upon almost exclusively in case management. Such a course of action does not take into account the limitations of a single diagnostic procedure and the errors which are inherent in its interpretation.

That the interpretation of a single roentgenogram of the chest is subject to considerable error has been demonstrated in a number of studies (1–4). There are errors both in detecting shadows and in evaluating their significance. In interpreting routine mass survey films, as many as 30 per cent of roentgenograms showing evidence of disease may escape detection at a single reading while 1 or 2 per cent of "negative" chests are interpreted incorrectly as showing evidence of disease. Even greater discrepancies are encountered in evaluating the *significance* of those lesions which are detected. Interpretations of single roentgenograms demonstrating the probable "activity" of the lesion are grossly inconsistent for any two readers and indeed for two independent interpretations by the same reader. *It has been assumed*, however, *that it is possible to assess with a great degree of reliability the "activity" of a lesion from a comparison of two or more roentgenograms of the chest obtained at appropriate intervals.* It is this assumption which is being investigated in the present study.

It is possible that when changes between two roentgenograms are gross in terms of both the size and the "character" of the abnormal shadows, little difficulty will be encountered in evaluation. The perception of gross changes, however, is not sufficient for everyday practice. One of the objectives of treatment of a patient is to arrest the spread of his disease. It is of importance, therefore, to detect minimal changes in the disease process before major damage has been accomplished. The usefulness of roentgenograms, as of other diagnostic tests and clinical procedures, must therefore be assessed by the ability of the interpreter not only to detect gross changes but also to observe more moderate changes. It is not sufficient for a physician who observes a patient every three months to be able to note changes between two films taken at long intervals apart. It is of much greater significance to him to be able to diagnose the changes as they occur.

The present study was designed to evaluate how consistent the interpretations

of two single postero-anterior roentgenograms of the chest obtained three months apart are in providing estimates of changes in the lesion. The reliability of the information obtained from roentgenographic interpretations *alone*, without reference to other clinical and laboratory data, was the subject of the investigation. The reliability of the roentgenographic data per se is the knowledge which is needed before the integration of the roentgenographic findings with other clinical and laboratory data properly can be performed. The basic method used in the present study is simple. Several readers independently estimated progression, regression, or stability on a group of serial roentgenograms, and their disagreements and self-contradictions were evaluated.

MATERIALS AND METHODS

The material on which the study is based consists of 150 pairs of 14 by 17-inch films of the chest of 150 patients with pulmonary tuberculosis taken approximately three months apart. All the identification markers on the films were covered and a new numbering system was used which identified the films and the sequence of each pair. By this means the readers knew which was the first and which was the second film, and judgment was made on the changes between the first and second films.

This group of films was interpreted independently by three phthisiologists and three radiologists.[3] After a lapse of some time and without knowledge of the results of the first interpretations, the same films were reinterpreted by the same readers. This provided a total of twelve independent readings on each pair. Since two readings were made by each of the readers, it was possible to study the consistency of the two interpretations of each reader as well as to compare the interpretations of each with those of the other five readers. These permit the determination of differences between readers, *inter-individual variation*, as well as inconsistencies in the readings of the same individual, *intra-individual variation*.

Considerable experimentation preceded the final study: first, in order to adopt as nearly as possible uniform methods of interpretation; second, to evolve the best classification list for use in the main study. The first objective, that of obtaining uniformity of interpretation, was obtained by independent and joint readings and discussions of a number of sets of films which were not included in the final study. In these discussions many problems were encountered and agreement was reached concerning procedures for handling them.

A brief outline of the conventions used is as follows:

1. If an extensive area of infiltration in a lung clears up between two examinations but a small fresh infiltrate develops, should this be classified as improvement, deterioration, or of no significant change? The group agreed that it should be classified as "worse" in view of the fresh exudate.

[3] The six readers were: Drs. James T. Harkness, Cowell Hospital, University of California; H. Corwin Hinshaw, Stanford University; Sidney J. Shipman, University of California; L. Henry Garland, Stanford University; Earl R. Miller, University of California; and Henry B. Zwerling, Alta Bates Hospital.

2. Should a decrease in size of a cavity with concomitant increase in the extent of infiltration be recorded as improvement or no change? How should the converse be recorded? It was agreed that decrease in the size of the cavity would be regarded as improvement but that apparent extension in the volume of diseased lung would be regarded as worsening. When the two are coexistent, individual judgment must be used as to preponderant change.
3. If multiple small cavities coalesce to form a larger one, how should this be classified? It was agreed that it should be classified as "worse."

In summary, the phrase "better" was used to indicate decrease in area of disease or decrease in density of disease or decrease in size of cavity. The phrase "worse" meant the reverse of the above. The phrase "no change" meant "no significant change in the extent or character of the lesion or lesions." This phrase was to be used also when changes observed in the two films were thought to be due to technical factors only.

In order to evolve a suitable classification list, preliminary experiments were conducted on three groups of 25 pairs of films to test different methods of reporting serial film interpretations. A more detailed discussion of the results of these preliminary trials is presented below. For the present, it is sufficient to say that as a result of these experiments the classification list adopted for the main study consisted of only three categories, *better*, *no change*, and *worse*.

Selection of material to be used: Selection of material to be used in the study was a very important problem. It was obviously desirable to have a set of films on a representative group of patients in order that the results of the study could be projected to a specified, clearly defined universe of patients with tuberculosis. It is, however, very difficult to attain this objective. Upon reflection it will become evident that it is almost impossible to select a group of patients which could in any way be considered a random sample of all patients with tuberculosis. The totality of all patients afflicted with the disease encompasses a great field ranging from those with very mild and stable disease encountered in follow-up clinics, through the group of ambulatory patients treated in clinics and private physicians' offices, to the more serious manifestations of the disease, including patients in the terminal stages treated in tuberculosis hospitals. Moreover, even if material were available for the selection of a random sample, complications would result from the fact that in a certain number of cases surgery is carried out during the three-month interval between the two films of the set. The films of such patients would be unusable for the present study.

After considering a number of possibilities the sample was selected as follows: A group of 47 pairs of films of patients who were receiving streptomycin in the interval between the first and the second films was obtained from the Public Health Service streptomycin study. A group of 60 pairs came from a sanatorium which admits patients mainly with chronic disease. Another set of 27 pairs came from a county hospital with an active tuberculosis service; and a group of 16 pairs was obtained from a private sanatorium. An attempt was made to obtain films for *consecutive admissions* in the last three groups, omitting only those of patients on whom surgery was performed during the first three months of their stay.

No claims are made that this group is a random sample of films of all possible patients with tuberculosis. The radiologists and phthisiologists participating

in this study believed, however, that the film pairs were not materially different from those which they are called upon to interpret in their routine practices. Similarly, the films were not selected from a technical point of view for the purposes of providing either a superior or inferior group of roentgenograms. Again the participating readers expressed their belief that the films of the set were technically neither better nor worse than those which they were accustomed to view in everyday practice.

OBSERVATIONS

Preliminary Trials

The main purpose of the preliminary trials was to derive a classification list best suited for the main study. As a minimum, the classification list must obviously enable the interpreter to separate the film pairs into three categories, those showing evidence of improvement, deterioration, or stability. Further possible refinement of the list relates to the degree of improvement or deterioration. Before proceeding with the main study it therefore became important to ascertain what degrees of refinement were appropriate.

Seven-category classification: Practice in classification varies but one method which is often used utilizes three degrees of change in either direction; namely, *slight*, *moderate*, and *marked*. Such a method of classification was employed in the comprehensive streptomycin study conducted by the Public Health Service. It appeared appropriate, therefore, to test this classification. Accordingly, in the first trial each reader separated the 25 pairs of films into seven categories composed of three groups of *better*, denoted by plus 1, plus 2, or plus 3; three degrees of *worse*, denoted by minus 1, minus 2, or minus 3; and the *no change* category, designated 0.

The results of this first trial showed that a seven-degree category is too fine and implies a degree of sensitivity which is not confirmed by actual practice. By the use of this classification list, the readers were more often in disagreement than in agreement. In only 48.2 per cent of the comparisons was the same category used by two readers to classify the same pair of films. Thus, if one reader classified a pair of films in one of these seven categories, there was better than a fifty-fifty chance that a second reader would place the same films in a different category.

This method of judgment is obviously too strict since a pair of readers are considered to be in disagreement even if both agree on direction of change but not on amount of change. Nevertheless, even if a less stringent requirement for agreement is utilized, the amount of disagreement still remains very high. Thus, if all degrees of *better* were considered to be in agreement (plus 1, plus 2, and plus 3 were taken to represent agreement) and, similarly, if all negative categories were considered synonymous, there still was a 38.3 per cent disagreement among the readers. It was obvious from this first trial that the seven-category classification would lead to very large inconsistencies and for this reason it was necessary to investigate methods of classification which would employ a smaller number of categories.

Five-category versus three-category classification: The second trial was devised to test the use of a five-category classification as compared to one which contains three categories. A second set of 25 pairs was interpreted independently by the use of two different classification lists. Each reader interpreted this set of films first by employing a five-category list consisting of the classifications *no change*, *questionably better*, *definitely better*, *questionably worse*, and *definitely worse*. Later, and without knowledge of the results of the first reading, the reader classified the same films by the use of a list which designated only direction but not amount of change, that is, by a list composed of only three categories *no change*, *better*, and *worse*. Since the same set of films was utilized for the two readings, it was first possible to compare the percentage disagreement which resulted from the use of the two classification methods. In addition, it was possible to combine in the analysis the *definite* and *questionable* categories of the first classification method in order to provide a direct comparison with the results obtained by the use of the three-category classification. Thus, an opportunity was provided to determine whether a five-category classification was superior to one consisting of only three categories in providing better agreement on direction of change even if it might not be satisfactory in estimating amount of change.

The five-category classification produced results which were as discouraging as those of the first trial. There was a 56.0 per cent disagreement between readers in classifying the film pairs in identical categories. With the method of classification employing three categories, there was a 37.5 per cent disagreement between the readers. This comparison was obviously not strictly valid because in the first instance two readers were considered to be in disagreement even if their judgment on direction of change was the same but differed only on degree of change. It was noteworthy, however, that, when the *questionable* categories were considered to be in agreement with the *definite* ones, the resultant disagreement was 41.6 per cent as compared with the 37.5 per cent when the three-degree classification was employed. In other words, the use of a five-category classification did not produce more consistent results than the use of a three-category classification even if the two were made comparable in estimating only direction and not amount of change.

From this second trial it can therefore be concluded that the more refined classification lists imply a degree of sensitivity which is not justified for the present study and that at best a judgment of direction of change is all that can reasonably be expected in the interpretation of the film pairs.

The unexpected high percentage of disagreement observed in the first two trials posed the question whether this might not be due to a small group of difficult films which might have been included in these two sets. On most films, however, the readers might be in much closer agreement than is indicated by the above percentages. In addition, the question arose whether the difficulty resulted from uncertainty in evaluating changes in character or quality or if similar difficulty would arise in judging changes in extent or quantity. Accordingly, a third trial was undertaken in an attempt to answer these questions.

Judgment of character and extent of shadows and use of designation "indetermi-

nate": A set of 25 pairs of films was circularized twice among the readers. The three-category classification of *no change*, *better*, and *worse* was adopted. In addition, the reader was allowed to use the term *indeterminate* if he considered the films difficult and believed that it was not feasible to express a specific judgment relative to change on the basis of the two films. After the films were classified in the above categories from an over-all point of view, similar judgments were made separately on apparent changes in quality and in quantity.

An analysis of the results of this third trial showed that the inconsistencies in reading could not be ascribed to the presence of a few difficult pairs of films. This may be judged from the fact that *a reader was unable to agree with other readers or with himself as to which of the pairs of films were difficult.*

The number of pairs in which the *indeterminate* designation was used varied with the readers from zero to seven. There was not a single film pair that was called *indeterminate* by more than three of the six readers and of only three film pairs was the term used by as many as three readers. Neither was a single reader able to agree with himself as to which of the films were difficult to interpret. For example, one reader used the term *indeterminate* three times on his first reading and only once on his second. Moreover, the set of films interpreted *indeterminate* on the second reading was not included among those which he thought were difficult when he read them the first time.

Similar results can be cited for the other five readers. Moreover, eliminating comparisons in which the term *indeterminate* was used and basing the evaluation only on such interpretations as those in which the reader was willing to express a specific judgment, there was still a 28.7 per cent disagreement between readers. In view of this, it appeared that the term *indeterminate* was not likely to be helpful and consequently the simple three-category classification was adopted for the main study.

The third trial also indicated that the difficulty was not confined to judging changes in quality. It is true that more difficulty was encountered in evaluating changes in quality than those in quantity, but the latter were by no means negligible. In judging changes in the quality or character, the readers, paired one against the other, were in disagreement 52.8 per cent of the time. Nevertheless, the percentage of disagreement in judging changes in quantity (40.5 per cent) was approximately as great as that in evaluating progress of the disease as judged from the film as a whole (40.8 per cent).

Summary: On the basis of the analysis of the material presented above on these three trials, the group concluded that the interpretation of changes in serial films was not sufficiently sensitive to warrant the use of more refined methods of classification which attempt to estimate degree of change. At best, the readers could be expected to classify the film pairs according to direction of change, utilizing the three simple categories *better*, *no change*, and *worse*. Consequently, this method was adopted for the main study. It was also believed that little would be gained by expressing an evaluation of changes in quantity and quality. The decision was to be made on the basis of an over-all judgment of the two factors. However, because in a number of pairs it was noted that the evidence

provided from one of the lungs was contradictory to that exhibited by the other, *it was decided that in the main study the reader would express his judgment in three ways: first, based on the entire lung field and then, separately, for changes in the right lung and in the left lung.*

Inconsistency in Interpretation of Serial Roentgenograms of the Chest

A first impression of the magnitude of the problem of inconsistency in the interpretation of serial roentgenograms may be obtained from the range found among different readers in placing the 150 pairs of films into the three categories of *better*, *no change*, and *worse*. This is shown in table 1, based on the interpreta-

TABLE 1

Distribution of 150 Film Pairs in "Better", "No Change," and "Worse" Categories by Each Reader on Two Independent Readings

(Diagnosis Based on Entire Lung Field)

READER	READING	NUMBER OF FILM PAIRS DIAGNOSED AS:			
		Better	No change	Worse	Total
A	First	68	56	26	150
	Second	57	69	22	148*
B	First	62	55	33	150
	Second	74	52	24	150
C	First	69	52	29	150
	Second	70	55	20	145*
D	First	65	58	27	150
	Second	57	69	24	150
E	First	39	91	20	150
	Second	49	81	20	150
F	First	52	75	23	150
	Second	49	74	27	150
Range		39–74	52–91	20–33	
Mean		59.3	65.5	24.6	

* The difference between this figure and 150 is accounted for by films which the reader found to be not of diagnostic quality.

tions given of changes in the entire lung field. Thus, one reader found that only 20 of the 150 pairs belonged in the *worse* category while another placed 33 in the same category. Film pairs considered to exhibit *no change* ranged from 52 to 91. Likewise, according to the judgment of one reader there were only 39 pairs which showed improvement, while another reader found 74 such pairs (nearly twice as many). Moreover, the 74 put in the category *better* by reader B did not contain all of the 39 which were so classified by reader E. A review of the numbers presented by each of the readers shows also that there is considerable variation in the numbers put in the different categories by the same reader on two different occasions.

Total measure of variation between readers and for a single reader: The data in

table 1 present a rough indication of the inconsistency between readers and by each reader but they do not afford a total measure of the variation. In order to obtain an estimate of the latter, the judgment given by each reader on each pair of films must be compared with that expressed on the same pair by the same or a different reader. In each of these comparisons the two readings might be either in agreement or in disagreement.

It was important to determine whether the disagreements in classifying films existed among *all* readers or only among some of them. That the problem is not confined to only a few persons but is found in all six readers may be judged from table 2. This table shows the number of pairs of films in which each one of the readers disagreed with each of the five others in the first reading of the pairs as

TABLE 2

Number of Disagreements of Each Reader with Himself and with Each of the Other Five Readers in Interpreting 150 Film Pairs

(Diagnosis Based on Entire Lung Field; Comparison Between Readers Based on First Readings Only)

WITH READER	NUMBER OF DISAGREEMENTS OF READER					
	A	B	C	D	E	F
A	*33*	44	38	47	55	49
B	44	*43*	42	52	56	50
C	38	42	*29*	46	53	48
D	47	52	46	*38*	55	48
E	55	56	53	55	*30*	42
F	49	50	48	48	42	*25*
Mean number of disagreements with other readers	46.6	48.8	45.4	49.6	52.2	47.4

well as the number with which he was in disagreement with himself in his own second readings. *In toto*, there are 15 comparisons between readers, obtained by comparing each reader with each of the others, and six comparisons for individual readers obtained by comparing each reader with himself.

Two things are immediately obvious from the data in table 2. First, the problem of disagreement between readers was of considerable magnitude: The pair of readers who agreed best still disagreed on 38 pairs; the pair of readers who agreed least put 56 pairs in different categories. Second, this was not a result of great differences by one or two of the readers but was present to a considerable degree for each of the six. In addition, the degree of inconsistency of each man with himself was also very high, although it was slightly lower than when comparison was made between readers. The inconsistency was least for reader F who disagreed with himself in 25 of the 150 pairs and was the highest for reader B who disagreed with himself in 43 instances.

In order to obtain an estimate of the percentage of disagreement which may

be expected between two readers when they interpret serial roentgenograms, all the material available in the present study can be utilized. For each pair of films, four comparisons for each pair of readers are available. For example, the first reading of reader A can be compared to the first and second readings of reader B and the second reading of reader A can similarly be compared to the first and second readings of reader B. Since there are 15 ways of pairing the six readers against each other, a total of 60 comparisons of one reader against another is available for every pair of films. Thus, for the entire group of 150 pairs of films there is available a total of 60 multiplied by 150, or 9,000 comparisons.[4] The magnitude of inconsistency in interpretation can be obtained by dividing the number of comparisons which resulted in disagreement by the total number of comparisons. Thus, in the 8,931 usable comparisons, there were 6,245 instances in which the same symbol was used by two readers and 2,686 in which there was disagreement. There was, therefore, a 30.1 per cent disagreement between readers.

TABLE 3

Percentage of Disagreement Between Readers (Inter-Individual) and for an Individual Reader with Himself (Intra-Individual) in Interpreting 150 Film Pairs

(Diagnosis Based on Entire Lung Field)

COMPARISONS WHICH WERE:	INTER-INDIVIDUAL		INTRA-INDIVIDUAL	
	Number	Per cent	Number	Per cent
Disagreements	2,686	30.1	192	21.5
Agreements	6,245	69.9	701	78.5
Total	8,931	100.0	893	100.0

The ability of a reader to be consistent with himself in interpreting serial films can be obtained in a similar way. For each pair of films there are available six comparisons of a reader with himself obtained by comparing the first and second readings of each reader. The 150 pairs of films provide, therefore, 900 intra-individual comparisons.[5] The number of these which are in disagreement divided by the total number of comparisons provides an estimate of a reader's chances of disagreeing with himself. These are shown in table 3.

From the data in table 3 the first main result of the study can therefore be stated as follows. In judging a pair of films for evidence of progression, regression, or stability based on the entire lung field, *two readers are likely to disagree with each other in nearly one-third of the cases and a single reader is likely to disagree with himself in approximately one-fifth of the pairs.*

The factor of technique: It was thought desirable to investigate to what extent the relatively large error in evaluating serial roentgenograms is attributable to

[4] There were not exactly 9,000 comparisons because occasionally a reader found a pair of films of non-diagnostic quality. These comparisons were left out. The total number of usable comparisons was 8,931.

[5] There were actually 893 usable comparisons.

technical factors such as the quality of the films, or differences in positioning, or in respiration. It is difficult to study this phase in a completely satisfactory manner, and the present material provides only a very rough evaluation of the part played by "technique" in producing inconsistent interpretations.

The 150 pairs of films were obtained in many different institutions, and techniques were obviously not standardized. The only available information in this regard relates to data noted under "Remarks." The readers were requested to comment in this place when they considered a pair of films to be of poor technical quality or when they thought that any changes that might appear in the shadows on the roentgenogram were due to differences in technique and not to

TABLE 4

Percentage of Disagreement in Interpretation of 101 "Good Technique" and 49 "Poor Technique" Film Pairs in Comparisons Between Readers (Inter-Individual) and for an Individual Reader with Himself (Intra-Individual)

(Diagnoses Based on Entire Lung Field)

TYPE OF COMPARISONS	"GOOD TECHNIQUE"		"POOR TECHNIQUE"	
	Number	Per cent	Number	Per cent
Inter-Individuals				
Disagreements	1,606	26.7	1,080	37.0
Agreements	4,405	73.3	1,840	63.0
Total	6,011	100.0	2,920	100.0
Intra-Individual				
Disagreements	123	20.5	69	23.6
Agreements	478	79.5	223	76.4
Total	601	100.0	292	100.0

changes in the lesion. These comments provide an opportunity to separate the 150 pairs of films into two groups: one in which no reader in any of his readings noted such technical difficulties, and another in which one or more of the readers commented on some technical phase of the pair of films. There were 101 film pairs of the first type and 49 of the second.

The performance of the readers on these two groups of films can be determined. There were 1,080 disagreements among the 2,920 comparisons available on the 49 pairs on which some comment about poor technique was made by one or more of the readers. The percentage of disagreement in this case, therefore, was 37.0. In contrast, with the 101 film pairs where no comment was made about poor technique, the percentage of disagreement was only 26.7 (table 4). It may be said, therefore, that part of the difficulty of interpretation of serial films was due to technical features. However, these are by no means the sole factors responsible for differences in interpretation. The results presented in table 4 confirm the well-known fact that methods need to be developed to provide serial films which are technically comparable.

Sources of material: As was stated previously, the material used for this study cannot be considered to be a representative sample of films of all patients with tuberculosis and of all manifestations of the disease. It may, therefore, be desirable to investigate whether there are any differences in the percentage of disagreement depending on the source of material which made up the sample for the present study. It will be recalled that the set of 150 film pairs was assembled from four different sources: a sanatorium accepting patients mainly with chronic disease; patients receiving streptomycin treatment; a county hospital with an active tuberculosis service; and a private sanatorium. These will be referred to in the sequence by "sanatorium chronic," "streptomycin," "county hospital," and "sanatorium private," respectively.

TABLE 5

Distribution of Film Pairs According to Category Agreed on by Four or More Readers by Source of Film Pairs

(Diagnosis Based on Entire Lung Field; Only First Reading by Each Reader)

SOURCE OF MATERIAL	TOTAL NUMBER OF FILM PAIRS	NUMBER OF FILM PAIRS IN WHICH NO SINGLE CATEGORY WAS USED BY MORE THAN THREE READERS	CATEGORY USED BY FOUR OR MORE READERS							
			Number of films				Per cent			
			Total	Better	No change	Worse	Total	Better	No change	Worse
"Sanatorium chronic"	60	9	51	13	34	4	100.0	25.5	66.7	7.8
"Streptomycin"	47	11	36	24	8	4	100.0	66.7	22.2	11.1
"County hospital"	27	4	23	6	9	8	100.0	26.1	39.1	34.8
"Sanatorium private"	16	3	13	6	5	2	100.0	46.2	38.5	15.3
Total	150	27	123	49	56	18	100.0	39.8	45.6	14.6

It was first desirable to determine whether the film pairs from these four sources were differently distributed with respect to the three categories of *better*, *no change*, or *worse*. This was difficult because the only information available was the films themselves and, as is shown above, film interpretation was subject to considerable variation. For the purposes of the present discussion, the symbol used by a majority (four of the six readers in the first interpretation) was taken to represent the probable course of the disease in the corresponding patient. If no agreement was obtained by a majority of the readers on a film pair, the probable course of disease in the patient was considered to be indeterminate and was left out. This procedure made it possible to determine the percentage of distribution of the film pairs from the different sources in the categories *better*, *no change*, and *worse*.

It may be of interest to note, first, that for 27 of the 150 pairs no agreement on a symbol could be ascertained and that 11 of these came from the 47 pairs in

the "streptomycin" group. The remaining 123 pairs for which a major symbol could be established were distributed as follows: 49 pairs, or 39.8 per cent, were considered in the *better* category; 56 pairs, or 45.6 per cent, were in *no change;* and in 18 film pairs, or 14.6 per cent, the majority agreed on the *worse* category.

It may be seen from table 5 that the distribution relative to progression, regression, or stability was different for the four sources from which the material was obtained. Thus, the film pairs that came from "sanatorium chronic" contained a large proportion (66.7 per cent) which were stable and a very small proportion (7.8 per cent) which were in the *worse* category. The "streptomycin" films were characterized by the fact that they contained a very large proportion (66.7 per cent) in the *better* category. The films which were provided by the "county hospital" contained the largest proportion of films in the *worse* category (34.8 per cent), while those provided from "sanatorium private" contained a

TABLE 6

Percentage of Disagreement Inter-Individual and Intra-Individual According to Source of Film Pairs

(Diagnosis Based on Entire Lung Field)

SOURCE OF MATERIAL	PERCENTAGE OF DISAGREEMENT	
	Inter-individual	Intra-individual
"Sanatorium chronic"	32.3	24.8
"Streptomycin"	32.7	22.8
"County hospital"	25.9	14.6
"Sanatorium private"	21.2	16.8

relatively large number in the *better* category (46.2 per cent) and relatively few (15.3 per cent) in the *worse* category. It is seen, therefore, that the four groups represent four different types of material.

There were notable differences in the percentage of disagreement in these four types of material. In table 6 the percentage of inter- and intra-individual disagreements are shown separately for the groups coming from the four different sources. It is seen that the highest percentage of disagreements was found for the "sanatorium chronic" and the "streptomycin" groups, while the "county hospital" and "sanatorium private" material was apparently much easier to diagnose. It is perhaps unexpected to find that the groups which were heavily weighted with stable disease ("sanatorium chronic") and those exhibiting considerable improvement ("streptomycin") caused the greatest difficulty in interpretation.

Comparative analysis of interpretations of chest specialists and radiologists: Since the two specialties of radiology and phthisiology were equally represented among the six readers participating in this study, it was thought it would be interesting to compare the performances of the two groups. In so doing it was not the intention to imply that differences herein observed necessarily reflect those of the two specialties. Obviously the three radiologists participating in this

study do not claim to be a representative sample of all radiologists; nor does the performance of the three phthisiologists necessarily characterize the performance of all members of their group. Nevertheless, the comparison might be instructive if only for the purpose of stimulating similar comparisons in other studies.

Of immediate interest is a comparison of the group performance of the three phthisiologists against that of the group composed of the three radiologists. In attempting to obtain such a comparison, it becomes necessary to define a method for obtaining group interpretation on a pair of films. For present purposes this was accomplished by using majority opinion. In other words, if a film pair was

TABLE 7

A Comparison of Group Performance of Phthisiologists and Radiologists

Distribution of Film Pairs According to the Category Used in Four or More Readings of Phthisiologists Against the Category Used in Four or More Readings of Radiologists

(Diagnosis Based on Entire Lung Field)

PHTHISIOLOGISTS		RADIOLOGISTS				
Group opinion on category		Group opinion on category				
		Number of films with four or more agreements on category			At most three agreements	Total film pairs
		Better	No change	Worse		
4 or more agreements on category	Better	36	13	2	10	61
	No change	0	48	0	2	50
	Worse	1	2	17	1	21
At most three agreements		4	8	1	5	18
Total film pairs		41	71	20	18	150

interpreted by a certain symbol in four or more readings by the radiologists, it was considered as representing the opinion of the radiologists. Similarly, if a film pair was denoted in four or more readings of the phthisiologists as falling in one of the three categories, that category was taken to represent the opinion of the chest specialists on that film pair. It was not possible, however, to obtain by this method a group opinion on each film, for in certain cases there was no agreement in as many as four readings by a given group. These represent an indeterminate category for the group.

In table 7 is presented a comparison between the interpretations of the radiologists and those of the phthisiologists. A number of interesting points appear in analysis of the data in this table. Considering first the marginal totals, it appears that the radiologists as a group distributed the 150 film pairs in the various categories differently than did the chest specialists. The main difference is that the *phthisiologists were more inclined to observe improvement in two films than were the radiologists, while the latter were more likely to diagnose stability in*

the film pair than were the chest specialists. The latter as a group placed 61 films in the *better* category as against 41 put in the same category by the radiologists. On the other hand, only 50 film pairs were considered by the phthisiologists to exhibit *no change* while the radiologists found as many as 71 such pairs.

In 101 film pairs there was agreement in the group opinion of radiologists and phthisiologists. In 36 of these, the two groups agreed that the film pair was in the *better* category. In 48 there was agreement for *no change*, and 17 pairs were placed in the *worse* category by the two groups. In an additional 5 cases, no group agreement could be obtained on a definite classification of the film pair either by the three radiologists or by the three chest men. In the remaining 45 cases, the film pairs were put in different categories by the two groups. The greatest divergence was found in cases where the radiologists as a group con-

TABLE 8

Percentage of Inter-Individual and Intra-Individual Disagreement When the Readings of the Three Phthisiologists Were Compared with Each Other; When Those of the Three Radiologists Were Compared with Each Other; and When The Readings of Each Phthisiologist Were Compared with Those of Each Radiologist

(Diagnosis Based on Entire Lung Field)

TYPE OF COMPARISON AND SPECIALTY OF READERS	PERCENTAGE OF DISAGREEMENT
Inter-Individual	
All pairs	30.1
Phthisiologists	27.1
Radiologists	29.2
Phthisiologists and radiologists	31.4
Intra-Individual	
All pairs	21.5
Phthisiologists	23.7
Radiologists	19.3

sidered the film pairs to exhibit *no change*. Of the 71 cases in this category, the chest men agreed that there had been *no change* in only 48 cases; in 13, the phthisiologists thought that the lesion was *better*; in 2, that it was *worse*; and in 8, no agreement was reached by the chest men. In contrast, when the phthisiologists considered a film pair as exhibiting *no change*, the radiologists almost always placed the film in the same category. Great differences were noted also on the 61 film pairs which the phthisiologists considered improved. In these cases the radiologists concurred in only 36 instances; in 13, they gave the classification of *no change*; in 2, they considered the same films showed evidence of *worse*; and in 10 instances, no agreement could be obtained by a majority of the radiologists.

It may be noted that there were 3 instances in which there was complete disagreement between the two groups. For 2 film pairs, the radiologists as a group considered the lesion *worse* while the chest men as a group thought it was

better. In the other case, the reverse situation occurred in which the radiologists considered the case *better* and the chest men, *worse*. These 3 film pairs together with the 5 mentioned previously, in which neither the radiologists nor the chest men could agree on a single classification, are without a doubt the most difficult in this set of films. They were subsequently reviewed in conference by all six readers and in most instances the disagreements persisted even after considerable discussion.

It may also be of interest to determine the inter- and intra-individual variation in interpreting serial films separately for the two groups. This information is shown in table 8. It will be seen that the phthisiologists were somewhat less likely to differ with each other than were the radiologists while the inconsistency of an individual reader with himself (intra-individual variation) was smaller for the radiologists than for the chest specialists. Thus, a phthisiologist disagreed in 27.1 per cent of comparisons with another, while a radiologist disagreed with another radiologist in 29.2 per cent of the cases. The greatest variation was found when the readings of a phthisiologist were compared with those of a radiologist. Percentage of disagreement in this case was 31.4. On the other hand, a phthisiologist contradicted himself in 23.7 per cent of his readings, while a radiologist contradicted himself in 19.3 per cent of his interpretations.

Unilateral lesions: It will be recalled that, in addition to the judgment derived from the entire lung field, the readers stated their evaluation separately for the right lung and for the left lung. It becomes possible, therefore, to investigate to what extent the difficulty in interpretation is a result of the complications inherent in interpreting bilateral lesions. It was suspected that a large part of the inconsistency was due to the fact that in a considerable number of film pairs the evidence exhibited by one of the lungs was contradictory to that found in the other. In evaluating each lung separately this complication was greatly reduced, although not entirely eliminated since contradictory evidence is occasionally present in different parts of the same lung. An analysis of the performance of the readers separately for each lung is therefore indicated.

Of the 150 film pairs there were 22 in which no lesion was present on the left side and 11 in which no lesion was present on the right side. Consequently, the total number of film pairs where a lesion was present on the left side was 128 and the total number in which a lesion was present on the right side was 139. These provide material for estimating the probability of disagreement in judging progress of a lesion separately for the right lung and for the left lung. This is shown in table 9. Thus, of the 8,280 comparisons which were available on the 139 pairs of films with a lesion on the right side, 2,440 were disagreements. The percentage of disagreement, therefore, was 24.5. Similarly, the readers disagreed with each other in judging the lesion on the left side 28.5 per cent of the time. These figures were only slightly lower than the 30.1 percentage of disagreement found by the same readers in evaluating the progress of the lesion as judged from the entire lung field. From this comparison it may be concluded that the major reason for the disagreements in serial film interpretation in this series is not due to those film pairs in which contradictory evidence is produced by the two

lungs because the percentage of disagreement was almost as high when judgment was made on only one of the lungs.

The same conclusion is justified when intra-individual variation is considered because here also the probability of a reader's disagreeing with himself in judging progression on a single lung field is only slightly lower than that derived from evaluating the entire lung field (table 9).

Degree of disagreement: Since a three-category classification was used in this study, there were only two types of disagreement possible. One which may be denoted "simple disagreement" was such that one of the readings was *no change*

TABLE 9

Percentage of Inter-Individual and Intra-Individual Disagreement in Interpreting Changes in the Right Lung and in the Left Lung

TYPE OF COMPARISON	RIGHT LUNG*		LEFT LUNG†	
	Number	Per cent	Number	Per cent
Inter-Individual				
Disagreements	2,440	29.5	2,168	28.5
Agreements	5,840	70.5	5,433	71.5
Total	8,280	100.0	7,601	100.0
Intra-Individual				
Disagreements	172	20.8	159	20.9
Agreements	656	79.2	601	79.1
Total	828	100.0	760	100.0

* Based on 139 film pairs.
† Based on 128 film pairs.

and the other was either *better* or *worse*. The other type, which may be termed "complete disagreement," was such that one reading was *better* and the other, *worse*. It is obvious that most of the disagreements would be of the simple kind. For one thing, a complete disagreement was not possible if one of the readings was *no change* because in this case the only possible disagreement was that of the simple kind. Nevertheless, there were a number of comparisons which produced complete reversals.

Of the 8,931 comparisons which are available on the basis of judgment on the entire lung field, in 401 instances (4.5 per cent) disagreements of the complete type occurred; that is, where one reader called it *better* while the other thought it was getting *worse*. This value represents a conservative measurement for the reason noted previously. In order to measure the chances for a complete disagreement more satisfactorily, it was necessary to consider only such film pairs which were called either *better* or *worse* by one reader and to determine how often the second man called the same film pair by the opposite classification. Such analysis reveals that complete disagreements occurred in 10.4 per cent of

instances. In other words, when one reader classified a film either *better* or *worse*, there was a 10.4 per cent chance that a second reader would use the opposite classification. The probability that a single reader will reverse himself completely in a second reading was somewhat lower, but even here it was not negligible. It occurred in 3.1 per cent of all comparisons and in 6.7 per cent of instances when he called it one time *better* or *worse* (table 10).

It is noteworthy that there were 36 film pairs which were diagnosed *better* by some readers and *worse* by others. Of these, 29 film pairs were put in all three categories of *no change*, *better*, and *worse*.

TABLE 10

Percentage of Disagreements Which Were "Complete Disagreements" Based on All Comparisons and on Comparisons Which Exclude Readings of "No Change" by Type of Comparison Between Readers (Inter-Individual) and for an Individual Reader with Himself (Intra-Individual)

COMPARISONS RELATING TO	INTER-INDIVIDUAL		INTRA-INDIVIDUAL	
	Complete disagreements, per cent		Complete disagreements, per cent	
	Of all comparisons	Of comparisons which exclude "no change" readings	Of all comparisons	Of comparisons which exclude "no change" readings
Entire Lung Field	4.5	10.4	3.1	6.7
Right lung	1.8	5.6	1.2	3.4
Left lung	4.2	11.7	2.8	7.0
Quality of Films				
"Good technique"	4.9	11.2	3.5	7.5
"Poor technique"	3.6	8.6	2.4	5.0
Specialty of Readers				
Phthisiologists	5.4	10.5	4.7	9.1
Radiologists	3.0	8.1	1.6	3.8

It is interesting to note from table 10 that disagreements of the complete disagreement type occurred twice as often when reading the left lung alone as when interpreting the right lung.

It is also of interest to note that complete disagreement occurred somewhat more frequently among the 101 film pairs where no mention of "poor technique" was made than for the 49 pairs which contained such comments. In other words, the occurrence of complete disagreement cannot be attributed to technical factors. Disagreement occurred in the interpretation of shadows which were considered by the readers to represent real changes in the lesion.

Complete disagreement occurred relatively more frequently among chest specialists than among radiologists. Among the former, such disagreements occurred in 5.4 per cent of all comparisons while among the radiologists complete disagreement was recorded in 3.0 per cent of comparisons. This was due in part, however, to the fact that the radiologists used the term *no change* more often than did the phthisiologists and, therefore, could not completely reverse themselves as frequently. When comparison was made on the basis of such films as

TABLE 11

Distribution of 150 Pairs of Films According to the Maximum Number of Identical Readings Out of 12

(Diagnosis Based on Entire Lung Field)

NUMBER OF IDENTICAL READINGS	TOTAL	MAJOR SYMBOL		
		Better	No change	Worse
12	38	16	13	9
11	28	11	16	1
10	17	6	8	3
9	19	6	10	3
8	19	8	9	2
7	12	7	5	0
6	13*	3	3	1
5	4†	2	0	1
Total	150‡	59	64	20

* Includes six film pairs in which the major symbol was indeterminate (4 pairs 6NC 6B; 2 pairs 6NC 6W).

† Includes one film pair in which the major symbol was indeterminate (1 pair 5W 5B).

‡ Includes the seven film pairs described in * and †.

TABLE 12

Summary Table Presenting an Estimate of the Results of Readings by Two Different Readers on 100 Film Pairs; the Number of Readings Which Will Be Agreements, "Simple Disagreements," and "Complete Disagreements" According to a Number of Factors Discussed in the Text

COMPARISONS RELATING TO	NUMBER PER 100 DUAL READINGS			"COMPLETE DISAGREEMENTS" BASED ON COMPARISONS WHICH EXCLUDE READINGS OF "NO CHANGE"
	Agreements	"Simple disagreements"	"Complete disagreements"	
Entire Lung Field	69.9	25.6	4.5	10.4
Right lung	70.5	27.7	1.8	5.6
Left lung	71.5	24.3	4.2	11.7
Quality of Films				
"Good technique"	73.4	21.7	4.9	11.2
"Poor technique"	63.0	33.4	3.6	8.6
Specialty of Reader				
Phthisiologists	72.9	21.7	5.4	10.5
Radiologists	70.8	26.2	3.0	8.1
Source of Material				
"Sanatorium chronic"	67.7	29.5	2.8	10.7
"Streptomycin"	67.3	25.6	7.1	12.1
"County hospital"	74.1	20.8	5.1	10.0
"Sanatorium private"	78.9	18.7	2.4	4.7

were called *better* or *worse* by one reader, the probability that another would use the opposite classification was almost as great for the radiologists as for the chest men. In intra-individual comparisons it was also found that a phthisiologist was more often in complete disagreement with himself than was a radiologist, but this again was partly due to the fact that a radiologist diagnosed a film pair more often as *no change* than did a chest specialist.

TABLE 13

Summary Table Presenting an Estimate of the Results of Two Readings by the Same Reader on 100 Film Pairs; the Number of Readings Which Will be Agreements, "Simple Disagreements," and "Complete Disagreements" According to a Number of Factors Discussed in the Text

COMPARISONS RELATING TO	NUMBER PER 100 DUAL READINGS			"COMPLETE DISAGREEMENTS" BASED ON COMPARISONS WHICH EXCLUDE READINGS OF "NO CHANGE"
	Agreements	"Simple disagreements"	"Complete disagreements"	
Entire Lung Field	78.5	18.4	3.1	6.7
Right lung	79.2	19.6	1.2	3.4
Left lung	79.1	18.1	2.8	7.0
Quality of Films				
"Good technique"	79.5	17.0	3.5	7.5
"Poor technique"	76.3	21.3	2.4	5.0
Specialty of Reader				
Phthisiologists	76.3	19.0	4.7	9.1
Radiologists	80.6	17.8	1.6	3.8
Source of Material				
"Sanatorium chronic"	75.2	22.6	2.2	7.5
"Streptomycin"	77.3	17.4	5.3	8.5
"County hospital"	85.5	12.0	2.5	4.7
"Sanatorium private"	83.1	15.8	1.1	2.0

Group opinion: Because of the variation in interpreting serial films, it cannot easily be determined what the probable change status is of the film pairs that have been studied. In other words, how many of the 150 film pairs show evidence of improvement, how many indicate deterioration, and how many represent stability of the lesion? One method of obtaining an estimate of these figures is to use group opinion; that is, to consider the designation given most often in the 12 readings available for each pair as the one representing the most likely change status. With this procedure each reading of each reader is given weight equal to that of every other reading of the same or another reader.

The distribution of the 150 film pairs by this procedure is shown in table 11. In this table, the 150 film pairs are distributed according to the total number of identical readings which were obtained in the 12 interpretations which were made for each. Thus, a film pair which was diagnosed the same by all six readers in all of the readings will have 12 identical readings. One in which 11 of the readings

were identical, with a single reader placing it in a different category in one of his readings, will have 11 identical readings, and so on. The least number of identical readings possible is 4 since there were 12 readings and three categories. There were 38 pairs in which the 12 readings were identical. An additional 28 had 11 identical readings, and in 17 others 10 of the readings were identical. Thus, in 83, or more than one-half of the film pairs, there were at least 10 identical readings while for the remaining 67 cases there were at most 9 identical readings.

Summary: It may be desirable to bring together much of the information presented above in two tables, one presenting variations between the readers and the other self-contradiction by an individual reader. These data are presented in tables 12 and 13. The tables are constructed to show what may be expected when a set of 100 film pairs is interpreted by different readers (table 12) or interpreted twice by the same reader (table 13). The material is presented to show how many of the 100 readings will be in complete agreement; how many in "simple disagreement," that is, when one reading is *no change* and the other either *better* or *worse*; and how many will be in complete disagreement, namely, one reading will be *better* and the other *worse*. Such comparisons are shown for many of the factors discussed above.

DISCUSSION

The main finding in this study is that, in the evaluation of two single postero-anterior chest roentgenograms obtained three months apart, competent physicians of considerable experience are likely to disagree with each other in almost one-third of the cases, and a single reader is likely to disagree with himself in approximately one-fifth of the pairs. Since many an important clinical decision often rests on roentgenographic evidence, this revelation of insecure foundation is of great importance. This does not mean that roentgenograms are not useful. They still may be the most dependable single piece of evidence but they must not be taken as the sole criterion of the patient's progress, nor can decisions rest on them alone. The dynamic status of pulmonary lesions cannot be determined without many observations in addition to the comparison of two single roentgenograms of the chest. Whenever all available procedures, such as physical examination, bacteriologic study, and others, are not used in determining a diagnosis or prognosis, the physician is multiplying his chances of error.

In addition to utilizing other clinical procedures, this study should serve as a reminder that roentgenographic examination of the chest should not be limited to two single postero-anterior chest films made a few months apart. In radiologic practice many patients are often studied by multiple projections and fluoroscopies as well. Although no specific information is available on the extent to which this extra care may add to the reliability of roentgenographic evaluation, it may be assumed that these additional procedures are helpful in a significant proportion of cases when indicated.

It should also be emphasized that inconsistency in diagnosis is by no means limited to radiology. In fact, it is likely that roentgenography is one of the more

reliable and exact diagnostic procedures in medicine. It is only because radiology lends itself more readily to quantitative evaluation of the degree of error that discrepancies in roentgenographic interpretation have been demonstrated in recent years. From such evidence as appears in the literature (5, 6, 7), it is apparent that the same problem is present in many other diagnostic procedures. It is very likely that, if similar objective investigations were conducted on other clinical procedures, the degree of error found would be of similar, if not of greater, magnitude than that observed here.

As an immediate corollary of the present study, it is necessary to determine the factors which influence errors in film interpretation. The demonstration that technically unsatisfactory films are less reliably read reinforces the need to develop methods for reducing, so far as possible, technical differences in serial roentgenograms. It may be hoped that significant reductions of presently observed unreliability will result from standardizing technique not only in regard to exposure but also in the positioning and respiratory phases.

Another important problem relates to nomenclature. It is necessary to develop more dependable methods for classifying lesions on a single roentgenogram and to determine more reliable standards for evaluating the dynamic status of disease as reflected in serial films. In the attempts made in the preliminary trials of the present study to obtain greater uniformity, it became apparent that the problem of evaluating changes in serial films is closely allied to that of determining and classifying the character or quality of a lesion and its extent. The solution to these problems must await further investigation.

SUMMARY

In this study an attempt is made to assess the reliability of estimates of change in serial single postero-anterior roentgenograms of the chest. A set of 150 film pairs (14 by 17-inch) obtained three months apart were interpreted independently twice by each of three radiologists and three phthisiologists of considerable experience in their respective specialties. The following findings are recorded:

In judging a pair of films for evidence of progression, regression, or stability of disease in patients with pulmonary tuberculosis, two readers are likely to disagree with each other in almost one-third of the cases and a single reader is likely to contradict himself in approximately one-fifth of the cases.

A significant but relatively small part of the error in film interpretation results from variations in technical factors.

The major reason for disagreements in serial film interpretation is not due to film pairs in which contradictory evidence is produced by the two lungs. On the contrary, a reader disagrees with himself or with another reader almost as much in evaluating changes in a unilateral as in a bilateral lesion.

When a reader compares a pair of roentgenograms and decides that one is *better* or *worse*, the chances are that in approximately 10 per cent of the cases another reader will use the opposite classification; and the same reader is likely to completely reverse his original diag-

nosis in approximately 7 per cent of readings of the same pairs of films.

Two tables are included which present in summary form the results which may be expected when two readers interpret a set of 100 film pairs (table 12) and when such a set is interpreted independently twice by the same reader (table 13).

SUMARIO

Valuación del Papel de las Radiografías Torácicas Seriadas al Estudiar el Avance de la Enfermedad en los Tuberculosos Pulmonares

En este estudio tratóse de apreciar la exactitud de los cálculos relativos a las alteraciones observadas en las radiografías postero-anteriores aisladas en serie del tórax. Una serie de ciento cincuenta pares de radiografías de 35 x 42.5 cm., tomadas con tres meses de diferencia, fué interpretada por separado dos veces por tres radiólogos y tres tisiólogos de mucha experiencia en sus respectivas especialidades. Los siguientes son los hallazgos:

Al juzgar un par de radiografías en cuanto a signos de agravación, regresión o estabilización de la dolencia en tuberculosos pulmonares, es probable que dos lectores discrepen entre sí en casi la tercera parte de los casos y que un solo lector se contradiga a sí propio aproximadamente en la quinta parte de los casos.

Una significativa pero relativamente pequeña parte de los errores en la interpretación de las radiografías proviene de variaciones en los factores técnicos.

La gran causa de desacuerdo en la interpretación de las radiografías seriadas no radica en los pares en que los dos pulmones arrojan datos contradictorios; un solo lector discrepa casi tanto con sí propio o con otro lector al apreciar las alteraciones en una lesión uni- o bilateral.

Cuando un lector rotula un par de radiografías como "mejor" o "peor," lo más probable es que, en más de 10 por ciento de los casos, otro lector use la clasificación contraria, y es probable que el mismo lector cambie completamente su diagnóstico primitivo aproximadamente en 7 por ciento de las lecturas de los mismos pares de radiografías.

En el texto de este trabajo dos tablas sumarizan los resultados que cabe esperar cuando dos lectores interpretan una serie de cien pares de radiografías (tabla 12) y cuando la misma serie es interpretada por separado dos veces por el mismo lector (tabla 13).

RESUME

Une évaluation du rôle des radiogrammes en série du poumon pour apprécier l'évolution de la maladie chez les tuberculeux

Dans cette étude, on a tenté de déterminer la valeur qu'on peut accorder à l'interprétation des changements observés dans les radiogrammes du poumon faits en série en position antéro-postérieure. Un jeu de cent-cinquante clichés

de 35/42,5 cms. pris en double à trois mois d'intervalle ont été séparément interprêtés à deux reprises par trois radiologues et trois phtisiologues particulièrement expérimentés. Le résultat des examens de ces clichés est noté:

Dans l'appréciation des deux clichés, pour y rechercher la preuve de l'évolution, de la régression ou de la stabilisation des lésions chez les malades atteints de tuberculose pulmonaire, il est probable que les deux lecteurs d'un cliché seront en désaccord dans près d'un tiers des cas et que l'un d'eux se contredira lui-même dans un-cinquième des cas environ.

Une part d'erreur significative, mais relativement réduite dans l'interprétation des résultats pour les deux radiogrammes, découle de variations dans les facteurs techniques.

La raison majeure pour le désaccord dans l'interprétation des films en série est due au fait que le lecteur de cliché est presqu'aussi souvent susceptible d'être en désaccord avec lui-même, ou avec un autre interprêtateur quand il s'agit d'évaluer les changements aussi bien pour les lésions unilatérales que hour des lésions bilatérales.

Quand celui qui interprête une paire de radiogrammes comme étant "meilleur" ou "pire", dans plus de 10% des cas il y a des chances pour qu'un autre soit d'un avis opposé et dans environ 7% des clichés étudiés, le même interprête d'une même paire de radiogrammes renverse son jugement.

Deux tableaux sont inclus dans le texte de cet article, ils présentent sous une forme sommaire les résultats qui peuvent être prévus quand deux lecteurs interprêtent un jeu de cent clichés pris en double (tableau 12) et quand cette série est interprétée séparément deux fois par le même lecteur.

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THE CLINICAL IMPORTANCE OF LESIONS UNDETECTED IN A MASS RADIOGRAPHIC SURVEY OF THE CHEST[1, 2]

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INTRODUCTION

To use any instrument effectively, it is necessary to establish and to appreciate its limitations. One of the purposes of mass roentgenographic surveys of the chest is to discover in those examined all persons with roentgenographic evidence of chest disease. This ideal has not been, and probably can never be, completely attained. It has been established that not all roentgenographically demonstrated lesions are detected by an individual reader during the course of survey reading. In approximately 30 per cent of persons with roentgenographic evidence of tuberculosis, the abnormal densities are overlooked in a single reading of routine mass survey material (1, 2, 3). This inability to detect all demonstrable lesions raises the question of their probable clinical significance. It is sometimes assumed that most of the lesions overlooked are of no clinical importance. If this were so, the problem of error in film interpretation would be of academic interest only. It therefore becomes of practical importance to determine whether the lesions overlooked are clinically active. In other words, does the mass survey nevertheless accomplish one of its major tasks, namely, to discover *all active* cases of pulmonary tuberculosis?

The present paper is an attempt to answer this question. It is a continuation of a previous investigation of the role of dual readings in mass roentgenographic surveys of the chest in which there were multiple independent readings of routine survey films by different persons (1). The number of readings was sufficiently large to ensure the discovery by one or more readers of nearly all persons with roentgenographic evidence of disease. Moreover, the multiple readings provided a number of films for analysis which contained abnormal densities which were overlooked by one or more readers.

The multiple independent interpretations of the mass survey films considered positive were correlated with the results of clinical and laboratory investigations. This provided data relating to the questions:

Are active lesions overlooked in mass surveys of the chest, and, if so, how frequently does this occur?

MATERIAL AND METHODS

The present study is based on material provided by an investigation of the role of dual readings in mass roentgenography of the chest. Detailed descriptions of the material may be found in a report by Yerushalmy and associates

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(1). There were 1,807 photofluorograms of entering college students which were interpreted independently ten times by six individual readers. On one or more occasions these multiple readings brought to light 254 films which were called "positive," i.e., contained abnormal shadows. All of these 254 persons returned for 14 by 17-inch films which were then reviewed, and it was decided by unanimous opinion of all the readers that 30 of these films revealed evidence of inflammatory disease which required further clinical study. By this procedure, 30 persons were identified who will be referred to in the following as "roentgenographically positive" patients. It was fortunate there was sufficient control of the students involved so that adequate clinical investigation could be undertaken in each case. Thus, there was provided the opportunity to perform, in addition to the usual history and physical examination, such specific studies as cutaneous reactivity to tuberculin, bacteriologic investigations, and other clinical and roentgenographic studies as were considered necessary. In each instance an attempt was made to establish a diagnosis, to determine the activity of the process if inflammatory, and to obtain follow-up observations for so long as one year whenever possible.

These various procedures provided information concerning the clinical status of the 30 "roentgenographically positive" patients by which they could be divided into "active" and "inactive" categories. While no clear-cut definition of activity can be formulated which is acceptable to all, for the purpose of the present study two sets of criteria are used. One relates to those with bacteriologic proof of tuberculosis who will henceforth be referred to as "bacteriologically active." The other consists of patients from whom no tubercle bacilli could be isolated at the time of the survey but who were either receiving active collapse therapy at the time or in whom active therapy was instituted as a result of the survey. These will be referred to as "clinically active."

RESULTS

As a result of the clinical and laboratory investigations on the "roentgenographically positive" patients, tubercle bacilli were isolated from 4 persons and in each instance this was confirmed by guinea pig inoculation. In addition to the 4 "bacteriologically active" instances there were 3 "clinically active" patients, 2 of whom were previously "bacteriologically active" but who were receiving active collapse therapy at the time of the study and another who was hospitalized for seven months as a result of the survey. All of the 7 showed a positive skin reaction to tuberculin. In the remaining 23 cases, the lesions were considered to be stable at the end of one year of observation.

It was possible to correlate the "activity" status of the 30 "roentgenographically positive" patients with the results of the original interpretations of photofluorograms. This indicated whether active lesions were overlooked. Moreover, the frequency with which active lesions were missed was compared with that of cases in which the lesions remained stable for one year.

Are Active Lesions Overlooked?

One of the most important questions in regard to subjective errors in film interpretation is whether all or most of the lesions not detected by a single

reader are innocuous in the sense that the lesion will remain stable and for all practical purposes can be considered inactive. Expressed differently, are there contained in this group of tuberculous lesions which are overlooked some which are in an active state? That the latter is true at times is demonstrated by the fact that 2 of the 4 "bacteriologically active" lesions were detected on only two of the ten readings on each photofluorogram; in addition, one of the 3 "clinically active" cases was detected on only one of the ten readings.

A more detailed account of these 7 "active" patients in which an abstract of the clinical record is contrasted with the performance of the individual readers on the interpretation of the photofluorograms is presented below. Readers E and F contributed single readings only; whereas the other readers reported each photofluorogram twice. It should be noted that each of the six individual readers overlooked at least one lesion.

Abstract of Clinical Record and the Interpretation of Photofluorograms by Six Readers on Seven Patients with "Active" Lesions, Four of Which Were "Bacteriologically Active" and Three "Clinically Active"

A. Patients with "Bacteriologically Active" Lesions

CASE NUMBER	ABSTRACT OF CLINICAL RECORD	INTERPRETATION OF PHOTOFLUOROGRAMS		
		Reader	Readings	
			First reading	Second reading
1	E. N., 23 years, female. Following detection of a parenchymal lesion during this survey, she developed chest pain and pleural effusion. Gastric lavage positive for tubercle bacilli by guinea pig inoculation. Left school for institutional care.	A	Negative	Negative
		B	Negative	Negative
		C	Negative	Positive
		D	Negative	Negative
		E	Positive	
		F	Negative	
	Photofluorogram Summary Reading: Two Positive, Eight Negative			
2	R. P. W., 23 years, male. In 1945, pleurisy with effusion. In 1946, 70 mm. film reported negative. Gastric lavage after detection by present survey positive for tubercle bacilli by guinea pig inoculation. A two-month follow-up film in June 1949 showed progression with cavity formation. Receiving institutional care.	A	Negative	Negative
		B	Positive	Positive
		C	Negative	Negative
		D	Negative	Negative
		E	Negative	
		F	Negative	
	Photofluorogram Summary Reading: Two Positive, Eight Negative			
3	P. S., 18 years, female. A survey film elsewhere, in December 1948, was reported positive but the family physician dismissed this as of no importance. The present photofluorogram was reported positive, and gastric lavage was positive for tubercle bacilli by guinea pig inoculation in April 1949. Gastric lavage negative in November 1949. Follow-up films show regression.	A	Positive	Positive
		B	Positive	Positive
		C	Positive	Positive
		D	Positive	Positive
		E	Negative	
		F	Positive	
	Photofluorogram Summary Reading: Nine Positive, One Negative			

CASE NUMBER	ABSTRACT OF CLINICAL RECORD	INTERPRETATION OF PHOTOFLUOROGRAMS		
		Reader	Readings	
			First reading	Second reading
4	J. C. B., 19 years, female. Knowledge of positive tuberculin and "scar" in lungs for ten years. Has had regular roentgenographic follow-up during this time. Again called positive during this present survey, and guinea pig inoculation of gastric washings were positive for tubercle bacilli at this time. Pneumothorax was started soon after and the patient has done well to December 1950.	A	Positive	Positive
		B	Positive	Positive
		C	Positive	Positive
		D	Positive	Positive
		E	Positive	
		F	Positive	
	Photofluorogram Summary Reading: Ten Positive			
	B. Patients with "Clinically Active" Lesions			
5	F. M., 19 years, male. "Positive" roentgenogram in 1943, but sputum negative for tubercle bacilli. Left phrenicectomy in 1945. Hospitalized 1946–1947, and gastric lavage positive for tubercle bacilli on culture. Pneumoperitoneum 1947–1950, including time of survey. One-year follow-up shows no change by roentgenogram, and no symptoms.	A	Positive	Positive
		B	Positive	Positive
		C	Positive	Positive
		D	Positive	Positive
		E	Positive	
		F	Positive	
	Photofluorogram Summary Reading: Ten Positive			
6	N. G., 23 years, male. Positive roentgenographic and bacteriologic evidence of tuberculosis five years before. Spread to opposite side two years later and pneumothorax for three years to and including time of survey. Sputum negative for tubercle bacilli by culture and guinea pig inoculation at time of survey. No change by roentgenography at one-year follow-up examination.	A	Negative	Negative
		B	Negative	Negative
		C	Negative	Negative
		D	Negative	Positive
		E	Negative	
		F	Negative	
	Photofluorogram Summary Reading: One Positive, Nine Negative			
7	A. D. T., 32 years, female. Pulmonary tuberculosis first diagnosed, August 1946, at the right apex. Spread to left, May 1947. No change until February 1949, at the time of the survey, when progression suspected. Was then hospitalized for seven months with slight regression on roentgenogram. No positive bacteriologic evidence of tuberculosis at any time.	A	Positive	Positive
		B	Positive	Positive
		C	Positive	Positive
		D	Positive	Positive
		E	Positive	
		F	Positive	
	Photofluorogram Summary Reading: Ten Positive			

How Often Are Active Lesions Overlooked?

The case summaries contain evidence that active tuberculous lesions may be overlooked. In addition, it is desirable to obtain a quantitative expression of

the probability of overlooking an "active" lesion as compared with the chance of overlooking an "inactive" lesion. Even though the present material is not large enough to yield reliable estimates of these probabilities, it may be worthwhile, nevertheless, to present a summary of the available material.

Such a comparison is presented in table 1. An over-all percentage of overlooking a given lesion can be obtained by the following considerations. There were ten independent readings on each of 30 "roentgenographically positive" patients. Consequently there were 300 readings available, and if all lesions had been detected on each reading there would have been a total of 300 "positive" readings on these films. A measure of the probability of overlooking a lesion can be derived by obtaining the ratio of the "negative" readings out of the total of 300 possible "positive" readings.

TABLE 1

Percentage of "Roentgenographically Positive" Films Which Were Overlooked on Initial Photofluorograms According to Activity Status of the Patient's Lesion

ACTIVITY STATUS OF PATIENT'S LESION	NUMBER OF PATIENTS (a)	RESULTS OF PHOTOFLUOROGRAM INTERPRETATION 10 READINGS ON EACH PHOTOFLUOROGRAM			
		Total readings (b)	Positive readings (c)	Negative readings (d)	Per cent overlooked $\frac{d}{b} \times 100$
"Active" Total	*7*	*70*	*44*	*26*	*37.1*
a) "Bacteriologically"	4	40	23	17	42.5
b) "Clinically"	3	30	21	9	30.0
"Inactive"	*23*	*230*	*161*	*69*	*30.0*
Total "Roentgenographically Positive"	30	300	205	95	31.7

Only 205 of the 300 readings were "positive," and in the remaining 95 instances the reader overlooked the lesion. Consequently the over-all percentage of errors on the entire material was 31.7. The same procedure is used to obtain the percentages of errors in the "active" and "inactive" categories. Thus, of the 230 possible "positive" readings for the 23 inactive cases, 161 were recorded "positive" and 69 as "negative," yielding an over-all percentage chance of overlooking such a lesion of 30.0. The percentage chance for error obtained in the same manner for the active lesions was 37.1; it was 42.5 per cent for the "bacteriologically active" cases, and 30.0 per cent for the "clinically active." Thus, it is apparent that the chance of overlooking a lesion is much the same whether the lesion is active or not. Moreover, approximately the same results are obtained whether the lesion is considered active on the basis of bacteriologic or clinical evidence.

SUMMARY

The present study provides data relating to whether an active tuberculous lesion is overlooked in mass roentgenographic surveys of the chest and how often this occurs. It has been demonstrated that "active" lesions are overlooked and,

although the study is based on relatively small numbers, it does indicate that an "active" lesion is just as liable to be overlooked as an "inactive" one.

The definition of activity used was based on bacteriologic and clinical criteria. No claim is made of the infallibility of these criteria for activity, but they conform to those used in the day-by-day practice of the physician or clinic responsible for these patients.

Viewed in the framework of the actual operation of the clinic, it may be stated that the main purpose for the mass survey which was instituted among the students was to detect precisely the 7 patients considered "active" in this study. The results of the present study show that the reader was at least as liable to overlook the "active" lesions in these 7 patients as the presumably innocuous lesions in the 23 other persons.

The problem of error in film interpretation in mass roentgenographic surveys of the chest is of extreme practical importance. The problem can be minimized to some extent by having the survey films read independently by more than one reader.

SUMARIO

La Importancia Clínica de las Lesiones Pasadas por Alto en una Encuesta Radiográfica Colectiva del Tórax

Este estudio facilita datos acerca de si se pasan por alto lesiones activas en las encuestas radiográficas colectivas del tórax y de con qué frecuencia sucede esto. Queda demostrado que se pasan por alto lesiones "activas," y aunque el estudio se basa en números relativamente bajos, sí indica que hay tantas probabilidades de pasar por alto una lesión "activa" como una inactiva.

La definición usada para actividad se basó en pautas bacteriológicas y clínicas. No se reclama infalibilidad para dichas pautas de la actividad, pero se conforman a las utilizadas en la práctica diaria del médico o la clínica que atienden a dichos enfermos.

En relación con el funcionamiento corriente de la clínica, cabe decir que el principal propósito de la encuesta colectiva llevada a cabo entre los estudiantes fué distinguir precisamente los siete enfermos considerados como activos en este estudio. Los resultados demuestran que el lector de las radiografías era por lo menos tan susceptible de pasar por alto esos 7 casos "activos" como los 23 inocuos.

El problema de los errores cometidos en la interpretación de las películas tomadas en las encuestas radiográficas colectivas del tórax reviste suma importancia práctica. Puede aminorarse hasta cierto punto haciendo que más de un lector estudie por separado las radiografías obtenidas en las encuestas.

RESUME

L'importance clinique de lésions pouvant passer inaperçues au cours de radiographies collectives systématiques du poumon

Cette étude fourni des données relatives aux lésions pulmonaires actives qui passent inaperçues au cours des radiographies collectives systématiques et à

leur incidence. Il a été démontré que des lésions "actives" ont échappé à l'examen et, bien que cette étude soit fondée sur un nombre de cas relativement restreint, elle indique qu'une lésion "active" peut aussi bien passer inaperçue qu'une lésion "inactive."

La définition de l'activité, dans ce travail, a été fondée sur des critères cliniques et bactériologiques. Les auteurs n'affirment pas l'infaillibilité de ces critères quant à l'activité de la lésion, toutefois ces critères sont conformes à ceux habituellement utilisés en pratique médicale journalière par ceux qui ont la responsabilité de cette catégorie de malades.

Il y a lieu de préciser que la principal objet de cette enquête clinique et des radiographies collectives, qui ont été pratiquées chez un groupe d'étudiants, était précisément de découvrir les sept malades considérés dans cette étude comme des cas "actifs." Les résultats de cette étude montrent que le lecteur des clichés a pu aussi bien manquer d'identifier 7 malades porteurs de lésions actives que 23 cas inactifs.

Le problème de l'erreur dans l'interprétation des radiographies collectives du poumon est d'une importance pratique extrême. Le problème peut être minimisé en faisant, indépendamment, interpréter les clichés par plusieurs spécialistes.

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ANALYSIS OF THE VENTILATORY DEFECT BY TIMED CAPACITY MEASUREMENTS[1,2,3]

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INTRODUCTION

Ventilation, or the mass displacement of air between the outside atmosphere and the interior of the lungs (1), is that aspect of pulmonary function of most immediate concern to clinicians. Defective ventilation may be the only impairment of pulmonary function while defective diffusion or distribution of gases within the lungs is almost always accompanied by a ventilatory defect as well. Furthermore, ventilatory insufficiency is most frequently the defect in diseases of immediate concern to the phthisiologist and thoracic surgeon. Only ventilatory function can be assessed relatively easily and quickly without the aid of much equipment and a research team. Finally, medical and surgical collapse of the lung and excision of pulmonary tissue are most likely to influence ventilation, and the end results of such therapy are easily followed by repeated ventilatory studies.

The maximal capacity of the lung to ventilate depends essentially upon two factors. The first of these is the total volume of gas or the maximal stroke volume which can be displaced by a single maximal respiratory effort. This total quantity of air measured as volume only is adequately expressed by the vital capacity. The second factor is the speed at which this volume can be exhaled. The speed depends upon two resistance factors: the resistance offered by the respiratory passages to the flow of air and the resistance offered by the lungs and thorax to a change in their shape incidental to the act of breathing. The resistance factors determine the time necessary for completion of the maximal expiratory effort. This is not effectively measured by the vital capacity since a patient with a normal stroke volume and a large resistance factor will eventually expire a normal amount of air if he can abstain for a sufficient length of time from taking in another breath. Normal ventilatory function depends on both an adequate stroke volume and on the absence of abnormal resistance factors.

[1] From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston; the Physiology Laboratory, Thoracic Surgery Service, Sanatorium Division of the Boston City Hospital, Mattapan; and the Department of Surgery, Boston University School of Medicine.

[2] Presented before the Medical Session as part of the symposium on *Laboratory and Other Basic Research* at the annual meeting of the National Tuberculosis Association, Cincinnati, Ohio, on May 16, 1951.

[3] This investigation was supported (in part) by research grants from the National Institutes of Health, Public Health Service; from the Committee on Medical Research and Therapy of the American Trudeau Society, medical section of the National Tuberculosis Association; and from the Foundation for the Study and Treatment of Thoracic and Related Diseases.

It is not surprising, therefore, that attempts to correlate the vital capacity with true tests of maximal ventilation have failed (2, 3, 4).

Dyspnea, the symptom of ventilatory insufficiency, depends largely on the maximal volume which can be moved per unit of time. But here again correlation between the degree of subjective dyspnea and the vital capacity has been poor (4, 5).

True maximal ventilatory ability is best measured clinically by the "maximum breathing capacity" (MBC). This is a voluntary test of maximum ventilation expressing the largest volume of air which can be moved in a unit of time (6). The maximum breathing capacity offers a good estimate of ventilation reserve, particularly if related to exercise ventilation (5). It is most useful in evaluating patients for collapse therapy and for intrathoracic surgical procedures.

As a ventilatory function test, however, the maximum breathing capacity has certain deficiencies. Low values do not indicate the cause of the ventilation defect which may be due to a decreased stroke volume, an increased resistance, or a combination of both. As the maximum breathing capacity measures both resistance and volume defects, however, and the vital capacity measures volume defects alone, a comparison of results from the two tests in any given patient should give a clue to the nature of the defect. Thus, if the maximum breathing capacity is greatly reduced and the vital capacity normal or nearly so, it can be presumed that ventilatory insufficiency is due to increased resistance; whereas if both are equally impaired, stroke volume is defective. The present writer has expressed this relationship by the fraction

$$\frac{\text{per cent of predicted maximum breathing capacity}}{\text{per cent of predicted vital capacity}}$$

and has designated the resulting number the air velocity index (3). In normal volunteers and in patients with stroke volume defects, the index is 1.0 or larger, while in patients with resistance defects the index is invariably less than 1.0 (3).

Gaubatz, reporting function studies before and after collapse therapy, included a figure expressing the number of liters per minute of maximum breathing capacity per liter of vital capacity. He observed that patients with relatively few liters of MBC per liter of vital capacity usually proved to be poor surgical risks (7). Matheson and associates have recently revived this fraction and have named it "capacity ratio" (8). The mean value for normal volunteers was 32.8 liters of maximum breathing capacity per liter of vital capacity. Only normal volunteers were evaluated in this manner but from theoretical considerations they believed that abnormalities of this "capacity ratio" should indicate deviation from normal in air flow resistance or muscular force.

Analysis of the ventilatory defect by the tests outlined is satisfactory for the physiology laboratory but it has several disadvantages for general hospital and ward use. Performance of both vital capacity and maximum breathing capacity tests are necessary. The latter test requires considerable equipment and training of both physician and patient. Furthermore, maximum breathing capacity requires a considerable effort on the part of the patient and does not

appear to give values truly reflecting maximal ventilatory ability in weak and very ill patients and in patients whose muscular effort is limited by a greatly reduced cardiac output. In patients with severe asthma and advanced emphysema there is evidence that the maximum breathing capacity is often less than maximal exercise ventilation. This suggests that the conscious, forced, expiratory efforts cause a reduction of breathing capacity by abnormally increasing the intrathoracic pressure (9, 10).

Another method involving observation of both volume and velocity is analysis of the vital capacity effort recorded by a spirometer on a fast-moving kymograph drum. Patients with marked bronchospasm or emphysema show a resistance defect depicted by a flattening of the expiratory slope of the vital capacity. The bronchospasm caused by administration of histamine or methacholine to asthmatic patients is often demonstrated only by changes in the expiratory slope while the total volume of air moved may remain unchanged (11). Bruce recorded vital capacity efforts in the manner outlined. He then divided the volume of the vital capacity by the recorded elapsed time and obtained "vital rates" which varied from 3 to 8 liters per second in normal subjects (12). He found that this "vital rate" correlated well with pulmonary disability.

PLAN OF INVESTIGATION

In this laboratory spirographic tracings are obtained routinely on a rapidly moving drum. In attempting to analyze them it was found that in patients with normal or nearly normal expiratory curves the slope was so steep during the first second of the expiratory effort that an accurate measure of the volume of air moved could not be obtained. Furthermore, a two-speed spirometer of the necessary size is so expensive that its use outside of the laboratory is impracticable. Lastly, the tedious analyses of tracings by trained personnel make the method unsuitable for large-scale use, such as for screening purposes.

It was decided, therefore, to introduce a time element into the ordinary vital capacity test. The first occasion for this attempt arose during a study of bronchial asthma (13). A large-bore three-way respiratory spigot was interposed between the spirometer and the patient's mouth. The onset of the patient's expiratory effort was timed, and the spigot was turned after three seconds, permitting the air expired after three seconds to escape. A "three-second" and later a "six-second" capacity were obtained in this manner and it was found that the three-second volume correlated much better with the maximum breathing capacity than did the total vital capacity (13). The method was suitable for patients with severe asthma or emphysema but others expired their air volume with such speed that the manipulation of the valve by hand introduced large errors in timing. Also the exact onset of the expiratory effort was often missed at the start of the timing. This led to errors in the measurement of the volume of air expired during short time intervals.

It was therefore planned to construct an instrument which would satisfy the following criteria:

1. It should automatically and accurately record a pre-set time interval of 0.1 to 10 seconds.

2. It should permit initiation of the timing cycle by the beginning of the patient's expiratory effort.

3. It should automatically record both the timed expiratory volume and the total vital capacity without recourse to an ink tracing requiring later analysis.

4. It should not introduce resistance to the system other than that of the tubing to the spirometer and the movement of the spirometer bell in the water.

5. It should be simple, foolproof, not much more expensive than an ordinary vital capacity spirometer, and should not require special training for its use.

The first apparatus constructed with the above criteria in mind consisted of two spirometers fitted with 1¼-inch, normally closed, solenoid valves which were joined at the mouthpiece end. This normally closed end was fitted with a small mercury manometer with two platinum electrodes. When the patient's expiratory effort raised the pressure in this blind end by approximately 1 mm. of mercury, contact was made between the platinum electrodes which initiated the timing cycle of an electronic timer and opened one of the solenoid valves. After a pre-set time interval the timer simultaneously closed the valve to the first spirometer and opened the valve to the other. The timed volume was collected in the first spirometer and the volume expired after that in the second spirometer. The total reading of the two spirometers was the total vital capacity. This system satisfied the first few criteria named above but did not comply with the fifth. It was a heavy apparatus and much more expensive than an ordinary vital capacity machine in that it required two spirometers and two costly solenoid valves. Most of the data presented in this study were obtained with this apparatus. During the past six months a new instrument has been built which satisfied not only the first four but also the fifth and last criteria. It is this apparatus which will be described in detail.

Methods

Timed vital capacity apparatus:[4] The only part of the standard vital capacity spirometer which was modified was the wheel which records the volume (figure 1). Three additions were made. A second pointer was added to the scale which is not moved by the stop on the wheel but, rather, by a small rod of a miniature solenoid. As soon as the current to the solenoid is interrupted, the rod retracts and this second pointer stops moving. In addition to the pointer and solenoid, a micro-switch was added which closes as soon as the wheel begins to turn. The spirometer with attachments is used in conjunction with an electronic timer which permits choice of any time interval from one to ten seconds. The timing cycle is initiated by the micro-switch on the wheel, and for the duration of the timing cycle the solenoid is made active and moves the second pointer on the scale. After completion of the timed interval the solenoid is inactivated and the second pointer comes to rest. The timed volume is therefore recorded by the second pointer and the total vital capacity is recorded by the standard pointer of the instrument. The timing cycle is initiated by the patient's expiratory effort, the onset of which closes the micro-switch. Technical details of the spirometer attachment have been described elsewhere (14).

[4] The entire instrument or the attachment alone may be obtained from Warren E. Collins, Inc., 555 Huntington Avenue, Boston, Massachusetts.

The timer: An electronic timer without lag was constructed because it is accurate at short time intervals and is activated without cumbersome mechanical equipment. It constitutes a modification by the author of a welding control timer (15). It is a resistance-capacitance timer using a single miniature thyratron tube. It can be easily and inexpensively constructed by any radio amateur or repair man. It has a long, trouble-free life, is unaffected by temperature, humidity, and line voltage changes, and repeats any time interval with an accuracy of $\pm\frac{1}{2}$ per cent. The timer (figure 1) has only two controls, an on-off switch

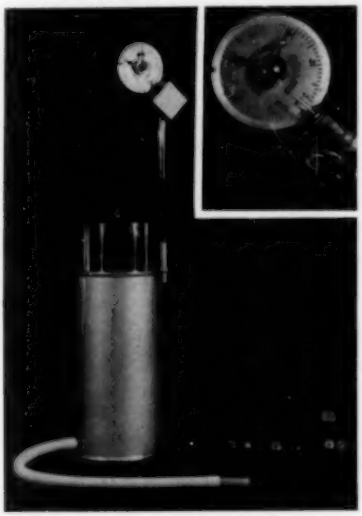

FIG. 1. Vital capacity spirometer with timed capacity attachment and electronic timer. The insert shows the timing device with the cover removed. On the left is the micro-switch which initiates the timed interval when the spirometer bell begins to rise. On the right is the midget solenoid which moves the added second pointer only while it is activated by the timer. The timer is unnecessarily elaborate. In addition to the on-off switch on the right and the time selector in the center, it has a time fine adjustment on the left and three pilot lamps.

and a time selector graduated from 1 to 10 seconds with stops at one-second intervals. The timers constructed for the present study have, in addition, an external means for fine adjustment of time intervals. This is unnecessary since it was found that the timer is completely stable and adjustment is necessary only when the tube is changed.

Data obtained from the timed vital capacity instrument: Initially, a number of time intervals from 0.1 to 10 seconds were tried. No patient was able to expire the entire vital capacity in less than 0.8 seconds. A large majority of all patients had expired the entire vital capacity in 4 seconds. The time intervals showing the largest variations between normal volunteers and patients were the one-, two-, and three-second intervals, and these were chosen for routine studies. After one or two trial expirations every patient had six vital capacity deter-

minations interrupted by suitable rest periods. Two determinations were made for each of the one-, two-, and three-second timed periods.

For statistical analysis the three efforts were chosen which resulted in the highest total vital capacity. Data are reported in three ways: the timed volume in cc., the timed volume as per cent of the total vital capacity, and the timed volume as per cent of the predicted total vital capacity.

Other concurrent pulmonary function tests: The only other studies made on all volunteers and patients with which the present study is concerned were the maximum breathing capacity, recording spirometry on a slowly moving kymograph drum, and residual volume determinations by the open circuit method. Relevant derived data were the air velocity index (3), the vital capacity as per cent of predicted and the maximum breathing capacity as per cent of predicted, calculated according to the Cournand regression formula (1). The detailed technique of these studies as performed in this laboratory and a number of other routine examinations performed on these as well as on all other patients have been described elsewhere (1, 16).

OBSERVATIONS

Thirty-five normal volunteers and 282 patients were studied on one or several occasions.

Normal Volunteers

The group of 35 normal subjects was equally divided between male and female and the patients were mostly in the younger age group. Their mean maximum breathing capacity was 123.9 liters per minute or 111.5 per cent of the predicted value, and their mean vital capacity was 3,634 cc. or 102.2 per cent of the predicted value (table 1). The prediction formula of Cournand for the maximum breathing capacity again resulted in values which were too low. Therefore the mean air velocity index of 1.11 was high (3).

The mean volume of air moved in the first second of the vital capacity effort was 3,008 cc., or 82.7 per cent of the total vital capacity and 84.6 per cent of the predicted total vital capacity (figure 2). These same figures for the first two seconds and the first three seconds of expiratory effort were 3,441 cc., (94.7 per cent of total vital capacity and 96.8 per cent of total predicted) and 3,532 cc. (97.2 per cent of total vital capacity and 99.3 per cent of total predicted vital capacity) (figure 2).

The mean velocity of air moved during the first second was 3,008 cc. per second or 180.5 liters per minute. The maximum breathing capacity was 123.9 liters per minute. Approximately half of this time was taken up by inspiratory effort. The mean expiratory velocity for the maximum breathing capacity was therefore 247.8 liters per minute, considerably more than for one-second single expiratory efforts. This would indicate that thirty breaths per minute for a maximum breathing capacity is too slow for the ideal effort, a fact recently confirmed experimentally by D'Silva and Mendel (17).

Figure 2 illustrates these findings in normal volunteers. No volunteer expired

less than 72 per cent of the total vital capacity in one second and less than 92 per cent in three seconds.

The smaller women tended to expire larger percentages of the total vital capacity during a given time interval than the larger males. Since the airway resistance for smaller subjects was smaller in proportion to the smaller volume exhaled, it was concluded that the external resistance to the air flow offered by the rubber tubing and the spirometer bell was relatively larger for subjects who were able to develop higher maximal air velocities. These differences were not observed among patients with ventilatory insufficiency.

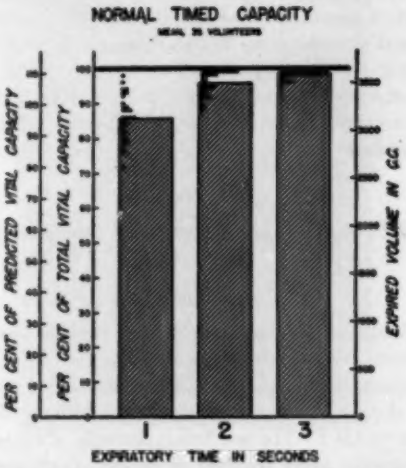

FIG. 2. Total vital capacity and one-second, two-second and three-second capacities of 35 normal volunteers. The shaded areas represent the mean volumes exhaled during the indicated time intervals. These volumes can be expressed as per cent of predicted vital capacity (first vertical scale), as per cent of total determined vital capacity (second vertical scale), or in cc. (third vertical scale). The dots represent performance of individual volunteers.

Effect of Artificial Expiratory Stenosis

A few volunteers made maximal expiratory efforts through an artificial external stenosis consisting of an iris diaphragm calibrated in millimeter diameter incorporated in the spirometer tubing. The result of one such study is illustrated in figure 3. A vertical line drawn at the 4 mm. diameter was thought to represent the smallest stenosis compatible with life. As the stenosis was increased, the total vital capacity remained unchanged up to 10 mm. It then rose slowly and reached a maximum at 4 mm., the severest clinical stenosis encountered in the living. The vital capacity then decreased rapidly and the subjects stated that they were unable to exhale all the air in their lungs because they could not hold their breath long enough. The "one-second capacity" proved to be the

most sensitive indicator of expiratory obstruction. A stenosis of 13 mm. caused the first decrease of this volume and a decrease from 20 mm. to 4 mm. caused the one-second volume to drop from 3,700 to 600 cc. The two- and three-second volumes were less sensitive to expiratory obstruction. No decrease in volume occurred down to 10 mm., and at 4 mm. the two-second volume was 1,800 cc. while the three-second volume was 3,000 cc. All three timed volumes showed a marked decrease with less than fatal expiratory obstruction of 4 mm. while the total vital capacity remained unaffected by such obstruction (figure 3).

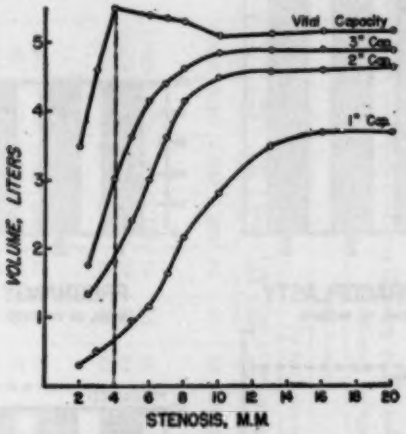

FIG. 3. The effect of varying degrees of expiratory stenosis on the total vital capacity and the one-, two-, and three-second volumes.

Special instructions for timed capacity determinations: Instructions to the patient for the timed volume tests were much the same as for ordinary vital capacity tests except that it was emphasized that, following the deepest possible inspiration, the air should be blown into the spirometer as *fast* as possible. The usual metal mouthpieces supplied with vital capacity spirometers have flattened ends to fit the shape of the lips. These were found to offer considerable resistance to the air stream, and their use resulted in abnormal expiratory patterns in normal volunteers with large vital capacities. Round metal mouthpieces or disposable cardboard tubes should be used with internal diameters no smaller than the spirometer inlet.

Timed Capacity Defect in Restrictive Ventilatory Insufficiency

Ventilatory insufficiency caused by a decreased stroke volume has been called restrictive (1).

Thoracoplasty: Thoracoplasty, in the absence of complicating emphysema, causes a purely restrictive type of pulmonary insufficiency. Mean values of ventilatory studies for 58 patients after thoracoplasty are shown in table 1. The maximum breathing capacity was reduced to 76.4 per cent of the predicted value and the vital capacity to 60.8 per cent of the predicted value. A relatively

greater loss of vital capacity than of maximum breathing capacity is the rule not only after thoracoplasty but following any long-standing reduction in stroke volume (3). The air velocity index of 1.26 was therefore larger than normal. The volume of air moved during the *first*, the *first two*, and the *first three* seconds

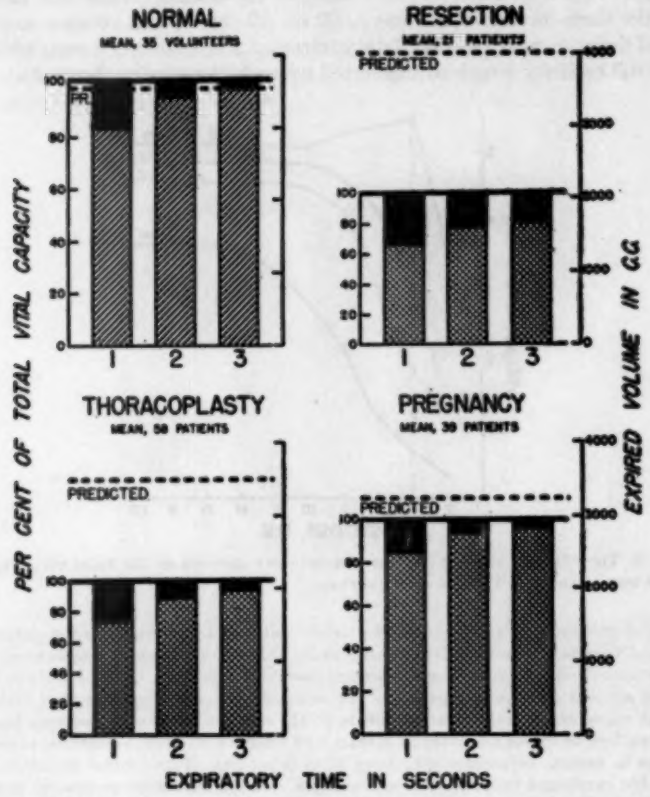

FIG. 4. The timed capacity defect in restrictive ventilatory insufficiency. Comparison is made with the normal timed capacities in the upper left corner.

of the vital capacity effort was much smaller than in normal volunteers. The percentage of the total vital capacity exhaled at these time intervals was 73.8, 88.5, and 92.6, respectively (figure 4). The decrease in the effectiveness of the stroke volume was only slight, whereas the decrease in the volume of the stroke was large. Analysis of data from individual patients showed that most patients studied six months after thoracoplasty showed no slowing of the air stream whatever, while those studied two weeks after operation showed some slowing

TABLE 1

Timed and Total Capacities and Maximum Breathing Capacity in Normal Volunteers and Patients with Restrictive and Obstructive Ventilatory Defects

DISEASE	NUMBER OF CASES	VITAL CAPACITY												MAXIMUM BREATHING CAPACITY LITERS PER MINUTE	MAXIMUM BREATHING CAPACITY PER CENT PREDICTED	AIR VELOCITY INDEX
		Cubic centimeters				Per cent predicted					Per cent of total					
		1 second	2 seconds	3 seconds	Total	1 second	2 seconds	3 seconds	Total	Predicted	1 second	2 seconds	3 seconds			
Normal volunteers	35	3,008	3,441	3,532	3,634	85	97	99	102.2	3,560	83	94	97	123.9	111.5	1.09
Restrictive Defect																
Thoracoplasty	58	1,562	1,874	1,960	2,118	45	54	56	60.8	3,480	74	89	93	78.2	76.4	1.26
Pregnancy	39	2,450	2,756	2,818	2,941	76	86	88	91.8	3,210	83	94	96	86.8	85.3	0.93
Resection	21	1,388	1,604	1,657	2,087	35	40	41	52.0	4,010	67	77	69	67.0	66.1	1.27
Obstructive Defect																
Bronchial asthma	28	1,069	1,460	1,756	2,482	31	42	50	71.2	3,490	43	59	71	41.0	38.5	0.54
Emphysema	40	931	1,270	1,509	2,220	25	34	41	60.2	3,690	42	57	68	37.5	36.6	0.61
Bronchostenosis	6	1,690	2,210	2,540	3,250	46	60	69	88.0	3,690	52	68	78	56.2	54.0	0.61

as well as greater variations in individual efforts. This slowing during maximal effort was due to hesitation by the patients because of postoperative pain. The effectiveness of the stroke may have been impaired also by paradoxical motion of the chest wall.

Pregnancy: Pregnancy produced a restrictive type of ventilatory insufficiency (18). Thirty-nine patients were studied at intervals during the second and third trimesters of pregnancy (table 1). The maximum breathing capacity was 85.3 per cent of the predicted value and the total vital capacity was 91.8 per cent, a slight but definite reduction of both maximal ventilation and single-stroke volume. The *first-*, *first two-*, and *first three*-second fractions of the total vital capacity were 83.3, 93.6, and 95.8 per cent of the total vital capacity, almost identical to the normal volunteer group (figure 4). There was no obstructive defect.

Pulmonary resection: Ventilatory function after pulmonary resection caused a ventilatory defect which was chiefly but not entirely characterized by a decreased stroke volume. Immediately after resection a compensatory overdistention of remaining lung tissue occurs. This may result in pulmonary emphysema if no steps are taken to limit the progressive overdistention (19). Data from patients after resection bear this out (table 1). The stroke volume was very much impaired as measured by a vital capacity with reduction to 52.0 per cent of the predicted value. Maximal ventilation was almost equally damaged since the maximum breathing capacity was only 66.1 per cent of the predicted value. The small but definite obstructive element was demonstrated by reduced fractions of the total vital capacity expired during the *first*, *first two*, and *first three* seconds of the effort. These were 66.5, 76.8, and 79.4 per cent of the determined total vital capacity, respectively (figure 4). Again postoperative pain may have been a factor in the relatively reduced expiratory velocities.

In figure 4 are summarized the findings in restrictive ventilatory insufficiency and a comparison is made with the normal values. In general, the total vital capacity is reduced in restrictive ventilatory insufficiency but the percentage of that vital capacity expired during the *first*, *first two*, and *first three* seconds is essentially normal.

Timed Capacity Defect in Obstructive Ventilatory Insufficiency

Ventilatory insufficiency caused predominantly by increased resistance has been called obstructive (1). The abnormal resistance may be due to an obstruction of the airway by bronchospasm as in bronchial asthma, by tuberculous tracheal or bronchial stenosis, or by partial occlusion of a major airway by tumor or lymph node. The resistance may be primarily caused by an abnormal resistance of lungs or chest wall to change in shape, as in pulmonary emphysema or scleroderma.

Bronchial asthma: Bronchial asthma in its early stages offers a good example of obstructive ventilatory insufficiency (table 1, figure 5). The mean vital capacity for 28 patients with moderate to severe bronchial asthma was 2,482 cc., or 71.2 per cent of the predicted value. The stroke volume was only moderately reduced, less so than after thoracoplasty or resection. The maximum breathing

capacity was 38.5 per cent of the predicted value, a much more severe reduction than was seen after surgery. The imbalance between insufficiency as measured by these two tests was expressed by an air velocity index of 0.54. Comparing this with the timed vital capacity, the obstructive defect was most strikingly

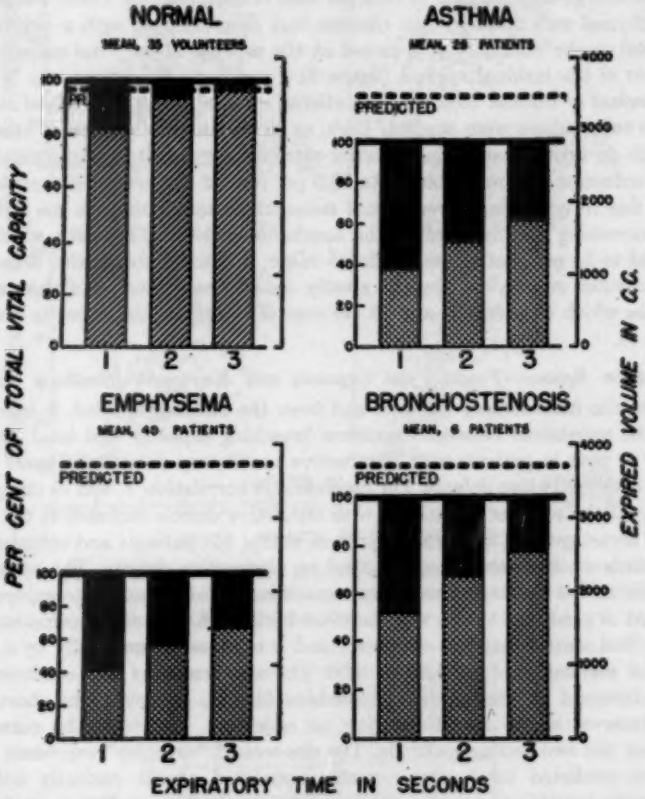

FIG. 5. The timed capacity defect in obstructive ventilatory insufficiency. Comparison is made with the values in the normal subjects presented in the upper left corner.

measured by the percentages of the total vital capacity expired during the *first*, *first two*, and *first three* seconds of the effort which were 43.1, 58.8, and 70.7 per cent, respectively (figure 5). These patients exhaled a smaller portion of the vital capacity in three seconds than patients with restrictive insufficiency in one second.

Pulmonary emphysema: The slowing of the expiratory air stream was somewhat more severe in 40 patients with pulmonary emphysema. The percentages

of total vital capacity exhaled during the three time periods were 41.9, 57.2, and 68.0. The maximum breathing capacity also was somewhat more severely reduced than in bronchial asthma (table 1). The ventilatory studies in this group differed greatly from the asthma group only in that the total vital capacity was also greatly reduced to 60.2 per cent of the predicted value. Pulmonary parenchymal and thoracic cage changes had progressed to such a degree that the total stroke volume was impaired at the expense of the vital capacity and in favor of the residual volume (figure 5).

Bronchial or tracheal stenosis: Six patients with bronchial or tracheal stenosis due to tuberculosis were studied. Here, as in the normal volunteers breathing through an artificial stenosis, the vital capacity showed little impairment. The small reduction in stroke volume to 88.0 per cent of the predicted was thought to be due to coexisting parenchymal tuberculosis rather than to the stricture. The narrowing greatly affected the maximum breathing capacity which was reduced to 54 per cent of the predicted value. A marked obstructive defect was demonstrated equally well by the greatly reduced one-, two-, and three-second volumes which were 52, 68, and 78 per cent of the total vital capacity (table 1, figure 5).

Correlation Between Timed Vital Capacity and Maximum Breathing Capacity

From the introductory remarks and from the patients studied, it is evident that the correlation between maximum breathing capacity and total vital capacity is poor in patients with obstructive ventilatory defects and good in patients with restrictive defects. The coefficient of correlation, r, will be the greater the larger the number of patients with restrictive defects included in the group under investigation (3, 4). In the present study, 153 patients and volunteers, or two-thirds of the entire group, showed no obstructive defects. The correlation between all the maximum breathing capacities and vital capacities expressed as per cent of predicted values was therefore fairly high. The relationship is shown in the first scatter diagram of figure 6 and is expressed numerically by a coefficient of correlation, r, of 0.56 ± 0.06. The significance of this coefficient has been discussed in greater detail elsewhere (4, 20). However, the shorter the time interval of the timed capacity air collection, the closer the correlation between the two testing methods. The one-second "capacity" expressed as per cent of predicted total vital capacity correlated almost perfectly with the maximum breathing capacity similarly expressed. The coefficient, r, for this group was 0.88 ± 0.06 (figure 6). Theoretically, the correlation should have been even better if a time interval corresponding to the ideal maximum breathing capacity rate had been chosen. This rate, at least in normal volunteers, is somewhat more than 60 breaths per minute (17) corresponding to a volume timed for 0.4 to 0.5 seconds. In practice it was found that time intervals of less than one second did not result in as accurately reproducible volumes.

The Timed Vital Capacity and the Air Velocity Index

Differentiation between a stroke volume defect and increased resistance to the expiratory effort can be made satisfactorily by both the timed capacity and the

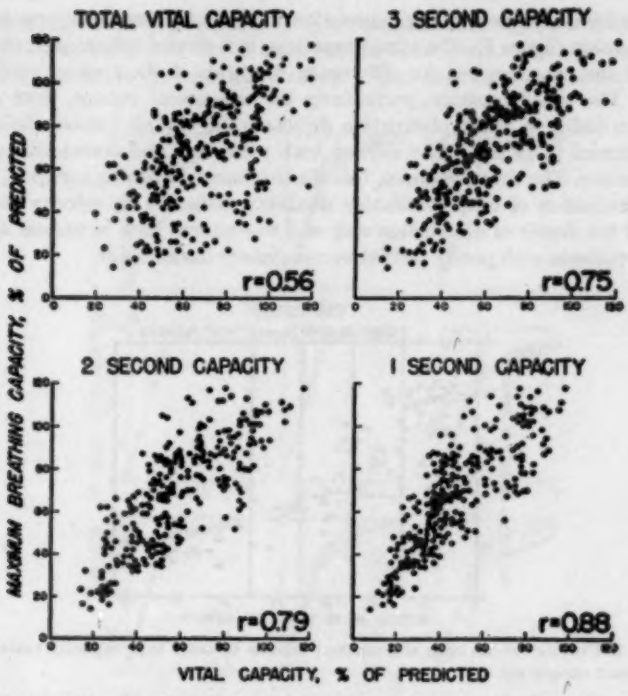

FIG. 6. Correlation between the total vital capacity and the maximum breathing capacity and the three timed capacities and the maximum breathing capacity. The coefficient of correlation, r, is indicated for each comparison.

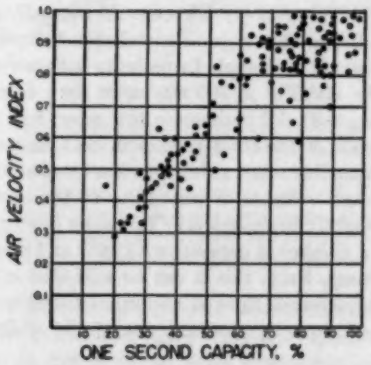

FIG. 7. Correlation between the air velocity index and the one-second capacity.

air velocity index. An excellent correlation was found between the two methods of evaluation (figure 7). The timed capacities had several advantages. Only one type of test was required for differential diagnosis of the type of ventilatory defect. The timed capacity, particularly the one-second volume, gave a more sensitive index of slight obstructive defects while the air velocity index was often normal in patients who showed both restrictive and obstructive ventilatory defects. The timed volumes, like the maximum breathing capacity, gave a direct indication of total ventilatory disability while the air velocity index indicated the degree of obstruction only and was normal both in normal subjects and in patients with purely restrictive ventilatory insufficiency.

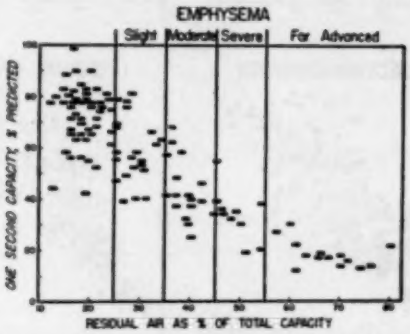

FIG. 8. Correlation between the residual volume to total lung capacity ratio and the one-second capacity.

Emphysema and the Timed Capacity

The severity of pulmonary emphysema may be expressed physiologically by the percentage of the total capacity of the lungs occupied by the residual volume, the so-called RV/TC ratio (1). This should normally not be more than 30 per cent (1). It was hoped that a good correlation between this ratio and the one-second capacity would be found. In patients with severe and far advanced emphysema where the RV/TC $\times$ 100 was more than 45 per cent, the correlation was excellent (figure 8). All patients in this group had a one-second volume of less than 40 per cent of the total predicted vital capacity. In patients with slight or no emphysema this relationship was less prominent, since a number of patients with one-second volumes of only 40 to 60 per cent of predicted values had normal or only slightly increased RV/TC ratios (figure 8). All patients with bronchostenosis and a number of patients with mild and recent bronchial asthma were in this latter group. From this it can be said that all patients with a significant degree of emphysema showed abnormal timed capacities, whereas an abnormally low timed capacity was not necessarily diagnostic of pulmonary emphysema.

Reproducibility of timed expiratory patterns: From the very onset of the study

it was noted that the percentage of the total vital capacity expired during the three time intervals was very constant in the same patients on repeated efforts. The first row (A) of figure 9 shows results of four studies made the same day on

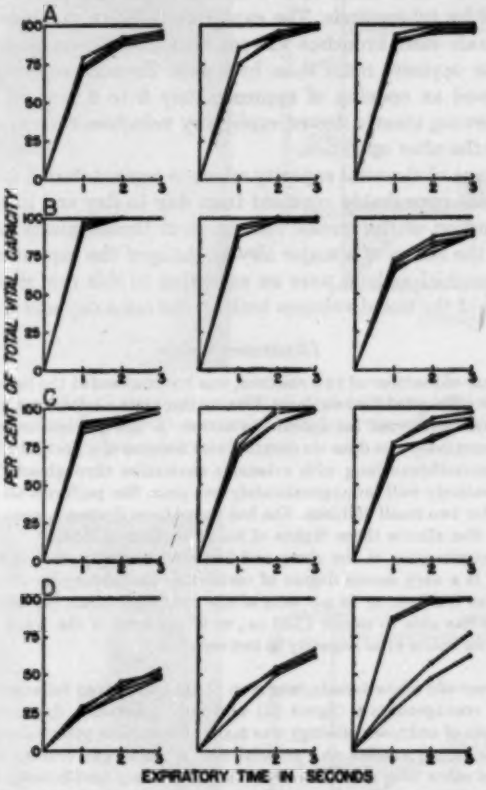

FIG. 9. Reproducibility of timed expiratory patterns. Row A shows results of four studies made the same day on each of 3 normal volunteers; row B shows curves of 3 normal volunteers studied repeatedly over the course of one year; row C shows expiratory patterns of 3 patients before, between stages, and after thoracoplasty; the first 2 patients of row D were repeatedly studied because of severe pulmonary emphysema; the last patient was studied twice before right pneumonectomy (upper curves) and twice after pneumonectomy during which a severe stenosis of the remaining main stem bronchus was produced.

3 normal volunteers. Most of the duplicate studies were unsuitable for reproduction since all four curves coincided completely and therefore could not be graphically superimposed. In row B of the same illustration, curves are shown for 3 volunteers studied repeatedly over the course of a year. Similar studies for pa-

tients studied before, between stages, and after thoracoplasty are shown in row C. The first two studies of row D show the greatly abnormal curves obtained on repeated occasions from 2 patients with severe pulmonary emphysema. The last patient of row D was studied on two occasions prior to pneumonectomy for a lung destroyed by tuberculosis. The expiratory pattern on these occasions was normal. The main stem bronchus was resected into the carina with a resulting stricture of the opposite main stem bronchus. Bronchoscopy two weeks after operation showed an opening of approximately 5 to 6 mm. in diameter. The two studies showing greatly slowed expiratory velocities were made three weeks and three months after operation.

The percentage of the vital capacity which is expired during accurately timed intervals remains remarkably constant from day to day and in the face of progressive diminution of the stroke volume as in thoracoplasty. An intervening diminution in the lumen of a major airway changed the expiratory pattern. Patients with bronchial asthma were an exception to this rule since they showed much variation of the timed volumes both on the same day and from day to day.

Illustrative Cases

A. D., a 26-year-old mother of two children, was hospitalized at the Sanatorium Division of the Boston City Hospital for two years. During this time a selective right apical five-rib thoracoplasty was performed for apical cavitation. A left pneumonectomy followed by left partial thoracoplasty was done six months later because of a partially destroyed, poorly re-expanded pneumothorax lung with extensive cavitation throughout. This patient has been home and entirely well for approximately one year. She performs all necessary housework and cares for two small children. She has never been dyspneic, even with moderately severe exercise. She climbs three flights of stairs without difficulty.

A recent roentgenogram of the chest and her vital capacity studies are illustrated in figure 10. There is a very severe degree of restrictive ventilatory insufficiency. The total vital capacity was 1,150 cc., or 34 per cent of the predicted value. No obstructive element existed since she was able to expire 1,030 cc., or 90 per cent of the total vital capacity in one second and the entire vital capacity in two seconds.

N. M., a 54-year-old white female, was seen at the physiology laboratory because of an abnormal chest roentgenogram (figure 11) and mild exertional dyspnea. A diagnosis of pulmonary fibrosis of unknown etiology was made. A complete pulmonary work-up, including exercise ventilation studies and arterial and alveolar gas tension studies, failed to reveal any defect other than a severe restrictive ventilatory insufficiency (figure 11).

The vital capacity was reduced to 1,150 cc., or 41 per cent of the predicted value. Here again there was no obstructive defect. The maximum breathing capacity was 66 liters per minute, or 99 per cent of the predicted value, and the patient exhaled 1,080 cc., or 94 per cent of the total vital capacity, in one second and the entire vital capacity in two seconds.

J. R., a 56-year-old white male, suffered from far advanced pulmonary emphysema. He had been hospitalized at the Boston City Hospital for seven weeks. He was unable to get out of bed because of severe dyspnea at rest. He required intermittent oxygen administration and supplementary intravenous and gastric-tube feeding because he was too short of breath to eat. The roentgenogram showed a picture characteristic of the disease (figure 12).

Ventilatory studies revealed a severe obstructive type of insufficiency. Although his vital capacity was 3,150 cc., or 74 per cent of the predicted value, he exhaled only 750 cc., or 24 per cent of the total volume, in one second (figure 12). The maximum breathing capacity

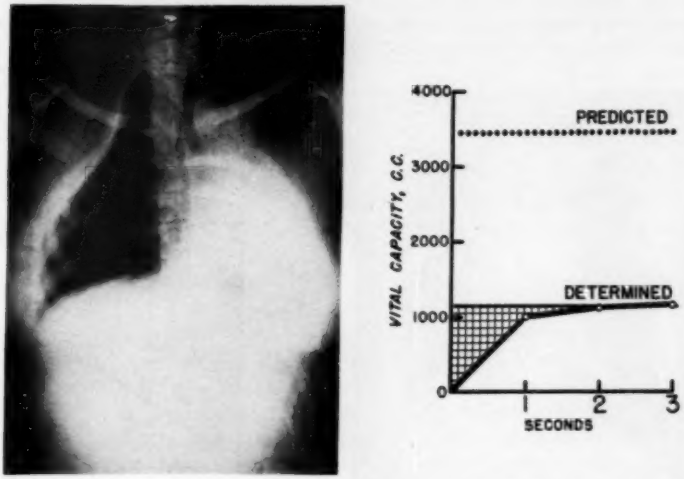

FIG. 10. Roentgenogram of the chest, predicted vital capacity, total and timed vital capacities of a 26-year-old female with restrictive ventilatory insufficiency due to thoracoplasty on the right and pneumonectomy on the left.

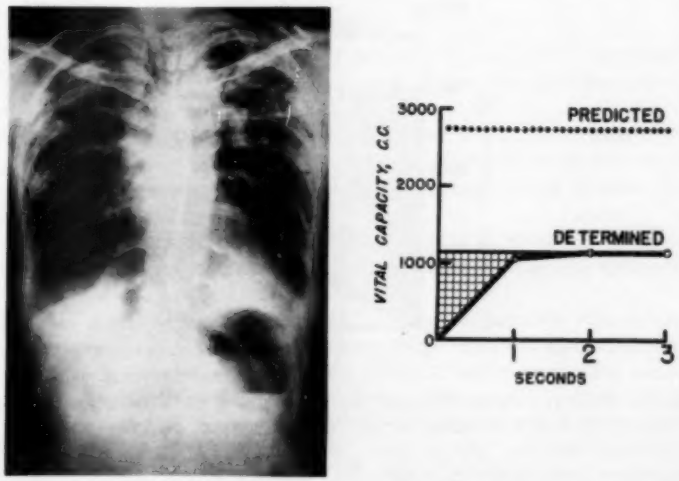

FIG. 11. Roentgenogram, predicted, total and timed vital capacities of a 54-year-old female with restrictive ventilatory insufficiency due to pulmonary fibrosis.

was 23 liters per minute, or 22 per cent of the predicted value. There was an excellent relation between the one-second volume and the maximum breathing capacity and no relation between the latter and the vital capacity. The air velocity index was only 0.30.

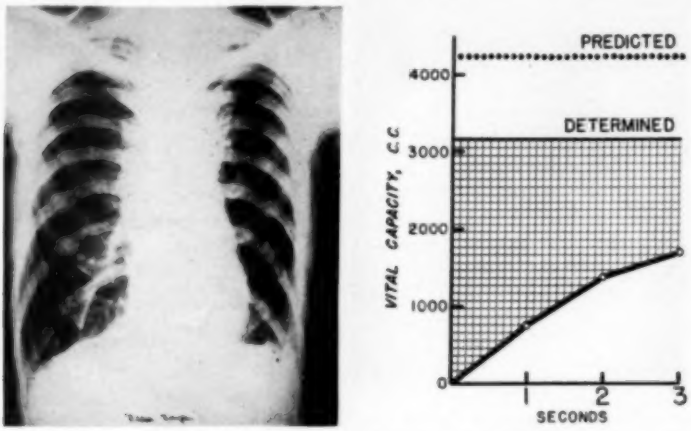

FIG. 12. Roentgenogram, predicted, total and timed vital capacities of a 56-year-old male with obstructive ventilatory insufficiency due to pulmonary emphysema.

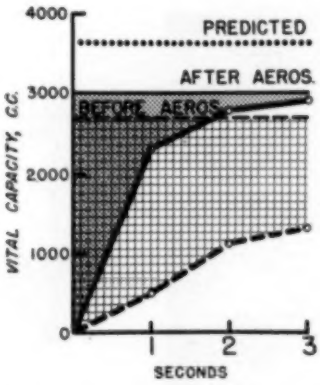

FIG. 13. Total and timed vital capacities of a 29-year-old asthmatic during an attack and after relief with a bronchodilator aerosol.

In addition to the ventilatory defect, this patient also had difficulty with gas distribution within the lung and gas diffusion across the alveolocapillary membrane. The RV/TC ratio was greatly increased, alveolar mixing was poor, arterial oxygen tension was somewhat low, and arterial carbon-dioxide tension was greatly elevated.

P. K., a 29-year-old male, was referred to the physiology laboratory for study of severe bronchial asthma of recent origin. The patient arrived at the laboratory in marked respiratory distress. He was severely dyspneic and slightly cyanotic. At that time his vital capacity was 2,700 cc., or 74 per cent of the predicted value. During the first second of effort only 420 cc., or 16 per cent of the total vital capacity, were exhaled; and 25 seconds were required to exhale the total volume. The patient was then given 1 cc. of a bronchodilator (isopropylnorepinephrine) by aerosol and was permitted to rest for approximately 20 minutes. At the end of that time he was essentially asymptomatic, and the vital capacity had increased to 3,000 cc.; this was only an 11 per cent improvement. However, during the first second of effort the patient exhaled 2,350 cc., or 78 per cent of the total effort, a 460 per cent improvement. The total volume was exhaled in 4 seconds in contrast to the 25 seconds before treatment.

COMMENT

By addition of an inexpensive attachment to the standard vital capacity machine, this instrument could be used for detection not only of decreased ventilatory stroke volume and restrictive ventilatory insufficiency but also for quantitative evaluation of resistance factors or obstructive ventilatory insufficiency. The research laboratory offers other and perhaps better opportunities for a detailed analysis of the ventilatory defect, such as the maximum breathing capacity, high-speed spirometry, pneumotachography, residual volume and alveolar pressure determinations, and others. These techniques are not available on the hospital ward, in the clinic, or in the physician's office, and they are not well suited for large-scale and screening studies. The timed vital capacity offers a simplified technique for analysis of ventilation when research methods are not available, and where large-scale and screening studies are required.

SUMMARY

The deficiencies of the vital capacity as a test for ventilatory function have been outlined, and it is suggested that the use of this test for evaluation of pulmonary function be abandoned.

An attachment for the vital capacity spirometer is described which automatically records both the total vital capacity and any volume expired during a pre-set time interval of 0.1 to 10 seconds. The timing cycle is initiated by the patient's expiratory effort.

Normal volunteers were able to expire 83 per cent of the total vital capacity during the first second of the effort, 94 per cent during the first two seconds, and 97 per cent during the first three seconds.

The total vital capacity was severely reduced in patients with restrictive ventilatory insufficiency but the timed percentages remained essentially normal. In patients with obstructive insufficiency, the total vital capacity was not markedly reduced but the percentages of the total vital capacity expired during the first three seconds were sharply reduced. In 28 patients with bronchial asthma these percentages were 43, 59, and 71 per cent for one, two, and three seconds. The same percentages in 40 patients with pulmonary emphysema were 42, 57, and 68.

Unlike the total vital capacity, the timed capacities correlated very well with the maximum breathing capacity, the air velocity index, and the RV/TC

ratio. Expiratory patterns of the same patients on repeated occasions varied very little. Unlike the total vital capacity, the timed capacities were very sensitive indicators of an artificially introduced stenosis of the airway.

The timed vital capacity should be useful on the hospital ward, in the clinic, and in the physician's office where a simple and inexpensive method for analysis of ventilation is needed. The timed vital capacity should be well suited for screening studies and large-scale investigations.

SUMARIO

Análisis de la Deficiencia Ventiladora por Mediciones Reguladas de la Capacidad

Bosquejadas las deficiencias de la capacidad vital como prueba de la función ventiladora, propónese el abandono de la misma en la justipreciación de la función pulmonar.

Descríbese un accesorio del espirómetro que registra automáticamente tanto la capacidad vital total como todo volumen de aire expirado durante un plazo de tiempo fijado de antemano de 0.1 a 10 segundos. El ciclo regulador comienza con el esfuerzo expiratorio del enfermo.

Los voluntarios normales pudieron exhalar 83 por ciento de la capacidad vital normal durante el primer segundo del esfuerzo, 94 por ciento durante los primeros dos segundos y 97 por ciento durante los primeros tres segundos.

La capacidad vital total disminuyó intensamente en los enfermos con insuficiencia ventiladora restrictiva, pero los porcentajes cronométricos permanecieron substancialmente normales. En los enfermos con insuficiencia obstructiva, la capacidad vital total no disminuyó en forma aguda, pero los porcentajes de la capacidad vital expirados durante los primeros tres segundos descendieron netamente. En 28 sujetos con asma bronquial, dichos porcentajes representaron 43, 59 y 71 para uno, dos y tres segundos. En 43 enfermos con enfisema pulmonar, esos porcentajes fueron de 42, 57 y 68.

En contraposición a la capacidad vital total, las capacidades reguladas en segundos correlacionaron muy bien con la capacidad respiratoria máxima, el índice de velocidad del aire y la razón VR/CR. Los patrones expiratorios de los mismos enfermos variaron muy poco en distintas ocasiones. En contraposición a la capacidad total, las capacidades reguladas resultaron ser indicadores muy sensibles de una estenosis de las vías aéreas, evocada artificialmente.

La capacidad vital regulada debe resultar útil en las salas de hospitales, la clínica y el consultorio médico siempre que se necesite un método sencillo y poco costoso para el análisis de la ventilación pulmonar. Debe prestarse igualmente para estudios de despistaje e investigaciones en gran escala.

RESUME

Analyse des troubles de la ventilation par la mesure de la capacité en fonction du temps

La déficience de la capacité respiratoire comme test de la fonction de ventilation a été esquissée; l'abandon de ce test d'évaluation de la fonction pulmonaire a été proposé.

Un appareil s'adaptant sur le spiromètre a été décrit. Cet appareil enregistre automatiquement la capacité respiratoire totale et le volume de l'air expiré dans un temps prédéterminé allant de un dixième de seconde à dix secondes. Le cycle chronométré est instauré par l'effort expiratoire du patient.

Des volontaires normaux ont été capables d'expirer 83% de la capacité respiratoire totale au cours de la première seconde de l'effort, 94% pendant les deux premières secondes et 97% pendant les trois premières secondes.

La capacité vitale était en totalité gravement réduite chez les malades présentant une insuffisance de ventilation par restriction du champ respiratoire, mais les pourcentages du volume d'air expiré mesurés en fonction du temps sont demeurés absolument normaux. Chez les malades présentant une insuffisance de ventilation par obstruction, le total de la capacité vitale n'était pas réduit de façon marquée mais les pourcentages obtenus en mesurant le volume d'air expiré au cours des trois premières secondes étaient nettement réduits. Chez 28 malades atteints d'asthme essentiel ces pourcentages mesurés pendant une, deux et trois secondes, étaient de 43, 59 et 71%. Les pourcentages correspondants chez 40 malades atteints d'emphysème pulmonaire étaient 42, 57 et 68%.

A l'encontre de ce qui se passe pour la capacité respiratoire totale, les capacités mesurées en fonction du temps correspondaient très bien à la capacité respiratoire maxima, à l'indice de vitesse de l'air expiré et au rapport étudié (volume d'air expiré dans un temps donné).

Le type expiratoire d'un même malade a peu varié au cours des examens répétés. Contrairement à la capacité respiratoire totale, les capacités en fonction du temps étaient des indicateurs très sensibles de l'oblitération acquise des voies respiratoires. La capacité respiratoire totale mesurée en fonction du temps semble devoir se montrer utile dans les salles d'hôpital, les cliniques et le cabinet du médecin, où une méthode simple et peu onéreuse pour l'analyse de la ventilation est nécessaire. La capacité vitale mesurée en fonction du temps paraît devoir convenir à l'enquête et aux opérations de dépistage systématique.

Acknowledgment

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SOME EFFECTS OF ADRENOCORTICOTROPIC HORMONE AND CORTISONE ON PULMONARY FUNCTION OF PATIENTS WITH OBSTRUCTIVE EMPHYSEMA[1,2]

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With the technical assistance of Dolores Lukas

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INTRODUCTION

The rapidly accumulating experience with cortisone and adrenocorticotropic hormone (ACTH) has included little that is relevant to chronic nontuberculous pulmonary diseases. Nevertheless, because of the potent influence exerted by cortisone and ACTH on the activity and reactivity of various tissues, there is reason to believe that these hormones might be of considerable aid in the management of many of the chronic nontuberculous lung diseases hitherto regarded as therapeutically hopeless.

Some information on the effects of these agents in the group of diseases associated with pulmonary fibrosis has become available recently. The administration of ACTH by Kennedy and his associates (1, 2) to two patients with advanced and disabling beryllium granulomatosis produced a remarkable remission of the disease as judged by symptomatology, chest roentgenograms, and pulmonary function studies. The response to ACTH in a case of silicosis was less dramatic, but pulmonary function was improved. West and his coworkers reported the results of therapy with ACTH and cortisone in three patients with diffuse interstitial fibrosis of the lungs (3). Pulmonary function underwent no change in one patient suffering from scleroderma, moderate improvement occurred in another with an unidentified type of granulomatosis, and marked improvement was noted in a third patient with fibrosis of undetermined etiology.

There is another group of pulmonary diseases characterized by the presence of bronchiolar obstruction. Prominent in this group are bronchial asthma and chronic obstructive pulmonary emphysema. Clinically, the efficacy of cortisone and ACTH in the management of bronchial asthma is now well known (4). The effects of these hormones on chronic obstructive emphysema, however, are in need of elucidation. There is increasing evidence that obstruction of the intrapulmonary airways (due to therapeutically intractable low-grade bronchial infection or unidentified respiratory allergens) plays a more important role in the pathogenesis of the physiologic defects of pulmonary emphysema than do the anatomic changes in the alveoli (5, 6, 7). It may be anticipated that an agent such as ACTH, which reduces the congestion, edema, and mucous production

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[3] Work completed during tenure of a Post-Graduate Research Fellowship of the National Heart Institute.

of diseased respiratory tract mucosa (8, 9) in addition to relieving bronchiolar spasm, would be of benefit in this disease.

The effects of ACTH or cortisone on chronic obstructive pulmonary emphysema, as well as on other chronic lung diseases, are best measured by changes in pulmonary function. The nature of these diseases is such that the physical examination and chest roentgenogram frequently do not reveal the true state and extent of coexisting alterations in function and consequently cannot be relied upon in evaluating the effects of the hormones. The following report deals with some effects of cortisone and ACTH on the pulmonary function of 9 patients with various types of chronic pulmonary disease, 7 of whom had considerable bronchiolar obstruction.

TABLE 1

Data on Patients Studied

PATIENT	AGE	SEX	DIAGNOSIS	BRONCHIOLAR OBSTRUCTION	HORMONE
A. vU.	52	F	Pulmonary emphysema	None	Cortisone
S. K.	44	F	Scleroderma with interstitial fibrosis of lungs	None	Cortisone
M. C.	53	M	Pulmonary emphysema	Moderate	ACTH
J. K.	62	M	Pulmonary emphysema	Marked	Cortisone
L. M.	45	F	Sarcoidosis of lungs	Moderate	Cortisone
J. McC.	50	M	Pulmonary fibrosis and emphysema, bronchiectasis, cor pulmonale	Marked	ACTH
J. M.	62	M	Bullous emphysema	Marked	Cortisone
G. O'N.	49	M	Bronchial asthma	Marked	ACTH
I. B.	45	F	Bronchial asthma	Marked	ACTH

PLAN OF INVESTIGATION

Subjects

Nine patients who ranged in age from 44 to 62 years were used in the investigation. The diagnoses of their illnesses included: pulmonary emphysema in 4 (in one of these the emphysema was of the bullous type); pulmonary fibrosis, emphysema, and cor pulmonale secondary to bronchiectasis in one; sarcoidosis of the lungs in one; interstitial pulmonary fibrosis of the lungs associated with scleroderma in one; and perennial bronchial asthma in 2 patients. Except for one of the subjects with emphysema and the patient with scleroderma, all subjects had evidence of moderate to marked bronchiolar obstruction as manifested by wheezing and rhonchi on examination of the lungs and by the response of their maximum breathing capacity to conventional bronchodilators. All patients were hospitalized during the course of the investigation and maintained under routine hospital conditions. Aside from the occasional administration of epinephrine or aminophylline in the 2 bronchial asthmatics and in one patient with emphysema (*J. K.*), no bronchodilating agent was used during hormone administration except for test purposes. Pertinent data on the subjects are presented in table 1. All subjects were studied a short time before and again

on the fourth to twenty-eighth days during administration of cortisone or ACTH. The patients with bronchial asthma were studied at times when they were free of symptoms of acute asthma.

Methods

Regimen of hormone administration: Cortisone, 100 to 200 mg., or ACTH, 40 to 240 mg., in four equally divided doses, was administered intramuscularly daily for varying periods of time. Hormone was discontinued after two weeks in the 2 patients without bronchiolar obstruction, the patient with sarcoidosis, and the patient with bronchiectasis. Because of excellent response, long-term hormone administration was continued in the other subjects on an outpatient basis.

Function techniques: Vital capacity and maximum breathing capacity (MBC) (10) were measured in all patients. Except in subjects *S. K.* and *A. vU.*, these measurements were repeated 5 to 10 minutes following the administration of 0.5 cc. of epinephrine HCl in 1:1,000 dilution subcutaneously or Vaponefrin[4] by nebulizer.

Complete lung volumes, ventilation, gas exchange, and blood gases were measured in 4 of the patients by methods previously described (10). Analysis of inspired and expired air, however, was performed with a 0.5 cc. Scholander microgas analyzer (11) instead of the Haldane apparatus. Normal and predicted values were obtained from the work cited above (10). All lung and ventilatory volumes were corrected to 37°C. saturated with water at ambient barometric pressure (BTPS).

Arterial blood was collected from an indwelling needle in the brachial artery. Blood pH was determined with the Cambridge research model pH meter at room temperature and corrected to 37°C. The tensions of carbon dioxide (pCO_2) and oxygen (pO_2) in the blood were measured by the method of Riley and associates (12), which in this laboratory provides duplicate checks of 4 mm. of mercury or better.

With the respiratory quotient of the expired air and the pCO_2 and pO_2 of the simultaneously collected arterial blood, it was possible to calculate alveolar oxygen tension and alveolar-arterial oxygen gradient (13). In addition, alveolar ventilation-perfusion analysis was performed (14). In this system, which relates the distribution of alveolar blood flow to alveolar ventilation, three categories of alveoli are considered: (*1*) alveoli which are ideally ventilated and ideally perfused with blood; (*2*) alveoli which are ventilated but not perfused and as such contribute to the *physiologic* dead space; and (*3*) alveoli which are perfused but not ventilated and as such are alveoli in which blood flow constitutes venous admixture to the ideally saturated blood emerging from alveoli in the first category.

The physiologic dead space, which included alveoli in the second category, is estimated by the formula:

$$\text{Dead Space} = \frac{\text{arterial } pCO_2 - \text{expired air } pCO_2}{\text{arterial } pCO_2 - \text{inspired air } pCO_2} \times \text{tidal volume} - \text{apparatus dead space.}$$

When the ratio of dead space to tidal volume exceeds 30 per cent, a larger number of alveoli than normal are acting as dead space.

The magnitude of alveoli in the third category is estimated by the formula:

$$\frac{\text{Venous admixture}}{\text{Total pulmonary blood flow}} = \frac{\text{Ideal alveolar saturation} - \text{arterial saturation}}{\text{Ideal alveolar saturation} - \text{mixed venous saturation}}$$

[4] Proprietary name of the Vaponefrin Company, Upper Derby, Pennsylvania, for preparation of a 2.25 per cent solution of racemic epinephrine hydrochloric acid.

In the absence of knowledge of the true mixed venous blood saturation, a value of 25 per cent lower than arterial saturation is assumed (14, 15). If the venous admixture exceeds 6 per cent of the total pulmonary blood flow, a larger proportion of alveoli than normal are not being ventilated but continue to be perfused with blood.

It should be recognized that varying degrees of disparity between magnitude of alveolar ventilation and perfusion may exist from area to area of the diseased lung. The net effect of this disparity on the expired air and arterial blood is expressed in the above system only in terms of alveoli in which this disparity is maximal, i.e., as alveoli which are either completely unventilated or alveoli completely not perfused.

No attempt was made to correct for the effect of the membrane component of alveolar-arterial oxygen gradient on venous admixture since only the relative size of venous admixture before and during hormone administration was sought.

RESULTS

Before hormone administration: In all patients ventilatory function, as measured by MBC, was greatly reduced. The improvement of MBC after use of a bronchodilator was particularly marked in 2 subjects with emphysema but was significant in all so tested except one of the patients with bronchial asthma. The response to epinephrine or Vaponefrin gave some index to the role played by obstruction of the bronchial tree in impairing the ventilatory ability of each patient.

Vital capacity was also reduced, although the degree of reduction was less than in MBC. Increments in vital capacity following epinephrine or Vaponefrin were notable in only 3 of the subjects. In the patient with scleroderma the pattern of pulmonary function differed from that observed in the other subjects in that she had a greatly restricted vital capacity and a normal MBC. Such discrepancy between vital capacity and ventilatory capacity in cases of scleroderma has been reported (16).

Hormone administration: During hormone administration all patients experienced some degree of improvement in dyspnea, cough, and sputum production associated with clearing of rhonchi and wheezes on examination. This improvement began on the second or third day of the hormone course and was usually maximal by the seventh day. Decrease of dyspnea was least remarkable in the subjects who had no signs or symptoms of obstruction of their intrapulmonary airways and was most marked in those who had pulmonary emphysema with evidence of considerable bronchiolar obstruction.

MBC and vital capacity measurements were repeated four to twenty-eight days after initiation of hormone administration. Marked improvement of MBC was observed in 2 patients with obstructive emphysema. In the other subjects, increases of MBC were of the same degree as that achieved transiently by a bronchodilator. The changes in vital capacity, in general, paralleled improvement in MBC; the degree of improvement of vital capacity, however, was usually less. In 3 instances, small reductions of vital capacity were observed; in 3 others, vital capacities attained normal values. Serial measurements per-

formed on some patients showed that maximal improvement in MBC and vital capacity occurred on the seventh to eighth days of ACTH or cortisone administration, thus paralleling the timing of the subjective improvement. When epinephrine or Vaponefrin was given during the course of hormone treatment, further increments in MBC were observed. In some instances the improvement of MBC following a bronchodilator was greater during hormone administration than before. The data on MBC and vital capacity are presented in tables 2 and 3 and in figure 1.

The spirographic tracings obtained during the performance of these tests are of interest. The pre-hormone tracings of all patients with clinical evidence of

TABLE 2

Maximum Breathing Capacity in Liters per Minute in Nine Patients with Chronic Pulmonary Disease Before and During ACTH or Cortisone Administration

PATIENT AND DIAGNOSIS		PREDICTED NORMAL VALUE	BEFORE HORMONE ADMINISTRATION	DURING HORMONE ADMINISTRATION	IMPROVEMENT
					per cent
A. vU., pulmonary emphysema		116	25	27	8
S. K., scleroderma		73	79	86	9
M. C., obstructive pulmonary emphysema	Before epinephrine	90	31	101	229
	After epinephrine		67	103	
J. K., obstructive pulmonary emphysema	Before Vaponefrin	90	34	64	88
	After Vaponefrin		48	92	
L. M., sarcoidosis	Before epinephrine	79	25	36	44
	After epinephrine		37	39	
J. McC., pulmonary fibrosis and emphysema, cor pulmonale	Before Vaponefrin	117	34	36	6
	After Vaponefrin		42	53	
J. M., bullous emphysema	Before epinephrine	91	25	33	36
	After epinephrine		30		
G. O'N., bronchial asthma	Before epinephrine	116	68	74	8
	After epinephrine		73	85	
I. B., bronchial asthma	Before epinephrine	72	42	48	14
	After epinephrine		45	56	

obstruction showed varying degrees of expiratory slowing and air trapping. MBC was performed in the inspiratory position with a shallow tidal volume and at a slow rate. During hormone administration these characteristics were eliminated or were much less pronounced.

Detailed Patient Studies

More extensive evaluation of pulmonary function was performed before and during hormone administration in 4 patients. Patients *M. C.* and *J. K.* will be considered together.

Patient *M. C.* had a six-year history of severe, paroxysmal, nonproductive cough and increasingly incapacitating dyspnea, which had caused him to give up his job. He

TABLE 3

Vital Capacity in Cubic Centimeters in Nine Patients with Chronic Pulmonary Disease Before and During ACTH or Cortisone Administration

PATIENT AND DIAGNOSIS		PREDICTED NORMAL VALUE	BEFORE HORMONE ADMINISTRATION	DURING HORMONE ADMINISTRATION	IMPROVEMENT
					per cent
A. vU., pulmonary emphysema		2,729	1,836	1,635	−11
S. K., scleroderma		2,796	900	979	9
M. C., obstructive pulmonary emphysema	Before epinephrine	3,329	1,746	3,397	95
	After epinephrine		2,642	3,364	
J. K., obstructive pulmonary emphysema	Before Vaponefrin	3,520	2,396	3,303	38
	After Vaponefrin		3,001	3,973	
L. M., sarcoidosis	Before epinephrine	2,715	1,504	2,082	31
	After epinephrine		1,795	2,037	
J. McC., pulmonary fibrosis and emphysema, cor pulmonale	Before Vaponefrin	3,666	1,493	1,470	−2
	After Vaponefrin		1,810	1,916	
J. M., bullous emphysema		3,467	1,464	2,073	42
G. O'N., bronchial asthma	Before epinephrine	3,992	3,749	4,446	19
	After epinephrine		3,711	4,511	
I. B., bronchial asthma	Before epinephrine	2,683	2,352	2,025	−14
	After epinephrine		2,373	2,362	

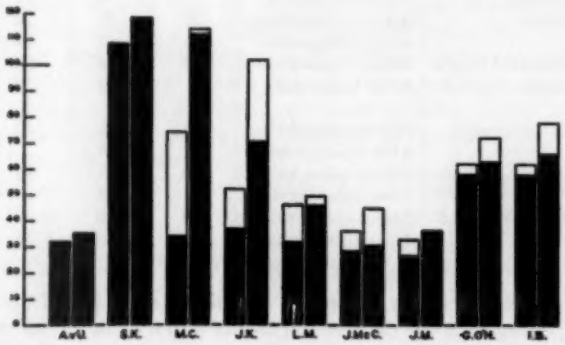

FIG. 1. Maximum breathing capacity in per cent of predicted value. The first of each pair of black vertical columns represents observed value before ACTH or cortisone administration; the second, the value during hormone administration. White columns are increases in MBC following Vaponefrin or epinephrine.

depended greatly on bronchodilators for partial control of his symptoms. He had also suffered from infrequent attacks of acute asthma, usually precipitated by upper respiratory infections.

Patient *J. K.* presented a history of chronic wheezing, more severe at night, and asso-

ciated with progressive dyspnea for two years. No evidence of cardiac decompensation was found to explain his symptoms.

TABLE 4

Pulmonary Function Studies—Patient M. C. (Male, 53 Years)

	BEFORE ACTH ADMINISTRATION	DURING ACTH ADMINISTRATION	PREDICTED NORMAL
1. Lung Volumes in cc.			
Vital capacity			
Before epinephrine	1,746	3,397	3,329
After epinephrine	2,642	3,364	3,329
Residual air	2,449	1,873	1,482
Total capacity	4,195	5,270	4,811
$\frac{\text{Residual air}}{\text{Total capacity}}$ in per cent	58.4	35.5	30.8
2. Maximum Breathing Capacity in liters per minute			
Before epinephrine	31	101	90
After epinephrine	67	103	90
Ventilation in L/min/m² B.S.A.			
Basal	3.6	8.1	3.9
Exercise	11.4	11.0	11.2
First minute recovery	12.4	13.9	14.5
Breathing reserve in per cent			
Basal	81	88	>92
First minute recovery	36	79	>75
3. Index of Intrapulmonary Mixing: Alveolar N_2 per cent	8.8	1.3	<2.5
Arterial Blood: Oxyhemoglobin saturation in per cent			
Basal	91.3 (88.1)	100.0	96
First minute recovery	93.5	100.0	96
Oxygen tension in mm. of mercury	66	93	95
Carbon dioxide tension in mm. of mercury	48	31	40
4. Inspired-alveolar oxygen gradient in mm. of mercury	55	28	48
Alveolar-arterial oxygen gradient in mm. of mercury	27	28	<12
$\frac{\text{Dead space}}{\text{Tidal volume}}$ in per cent	39	38	<30
$\frac{\text{Venous admixture}}{\text{Total pulmonary blood flow}}$ in per cent	15.3	5.3	<6
5. Oxygen Consumption in cc/min/m² B.S.A.			
Basal	107	125	132
Exercise	373	331	506

Comparable degrees of emphysema and pulmonary insufficiency were present in both of these patients (tables 4 and 5 and figures 2 and 3). The changes measured on the ninth and tenth days of ACTH administration in patient

M. C. and on the seventh and eighth days of cortisone administration in patient *J. K.* were striking. Vital capacities had increased to normal, and the residual

TABLE 5

Pulmonary Function Studies—Patient J. K. (Male, 62 Years)

	BEFORE CORTISONE ADMINISTRATION	DURING CORTISONE ADMINISTRATION	PREDICTED NORMAL
1. Lung Volumes in cc.			
Vital capacity			
Before Vaponefrin	2,396	3,303	3,520
After Vaponefrin	3,001	3,973	3,520
Residual air	2,382	2,090	1,567
Total capacity	4,778	5,393	5,087
$\frac{\text{Residual air}}{\text{Total capacity}}$ in per cent	49.9	38.7	30.8
2. Maximum Breathing Capacity in liters per minute			
Before Vaponefrin	34	64	90
After Vaponefrin	48	92	90
Ventilation in L/min/m² B.S.A.			
Basal	6.4	6.8	3.9
Exercise	15.4	13.3	11.2
First minute recovery	18.7	15.4	14.5
Breathing reserve in per cent			
Basal	69	82	>92
First minute recovery	10	59	>75
3. Index of Intrapulmonary Mixing: Alveolar N_2 per cent	7.1	5.7	<2.5
Arterial Blood: Oxyhemoglobin saturation in per cent			
Basal	91.1	93.2	96
First minute recovery	90.6	95.3	96
Oxygen tension in mm. of mercury	72	87	95
Carbon dioxide tension in mm. of mercury	46	40	40
4. Inspired-alveolar oxygen gradient in mm. of mercury	51	42	48
Alveolar-arterial oxygen gradient in mm. of mercury	23	18	<12
$\frac{\text{Dead space}}{\text{Tidal volume}}$ in per cent	56	38	<30
$\frac{\text{Venous admixture}}{\text{Total pulmonary blood flow}}$ in per cent	12.3	6.7	<6
5. Oxygen Consumption in cc/min/m² B.S.A.			
Basal	130	176	132
Exercise	493	416	506

air volumes had diminished to comprise only 35.5 and 38.7 per cent of the total capacities, respectively. These findings indicated a considerable reversal of the emphysematous state of the lungs of both patients (figure 2).

Ventilatory capacity attained the predicted value in patient *M. C.*; in patient

J. K., additional bronchodilation was needed before his ventilatory capacity reached normal. As a consequence of improvement of this function, neither

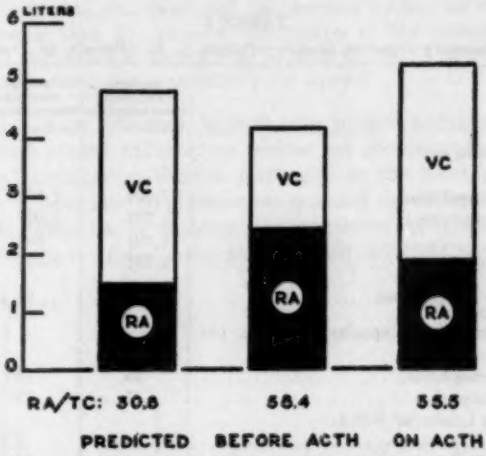

FIG. 2. Lung volumes in patient *M. C.*: VC = vital capacity; RA = residual air volume; TC = total capacity (VC plus RA); RA/TC = ratio of residual air to total capacity in per cent.

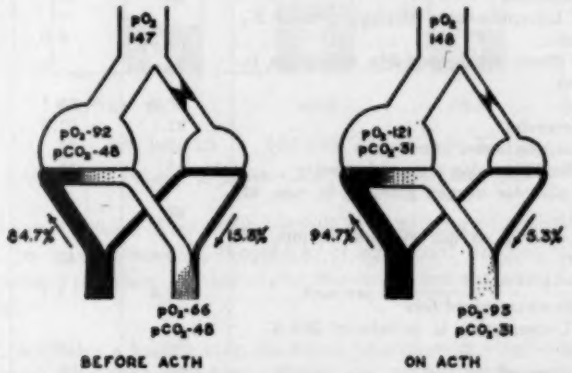

FIG. 3. Alveolar ventilation—perfusion relationships in patient *M. C.* Each schematic diagram shows mixed venous blood perfusing ideally ventilated alveoli on the left and unventilated alveoli with blocked airways on the right. Note decrease of venous admixture from 15.3 to 5.3 per cent during hormone administration as a result of decrease in unventilated alveoli with consequent increase of arterial pO_2 and decrease of arterial pCO_2.

patient experienced dyspnea during or after the standard exercise, whereas previously both had complained of severe dyspnea.

Alveolorespiratory function was also improved. As shown by the changes in the indices of intrapulmonary mixing and the decrease of dead space/tidal

TABLE 6

Pulmonary Function Studies—Patient L. M. (Female, 45 Years)

	BEFORE CORTISONE ADMINISTRATION	DURING CORTISONE ADMINISTRATION	PREDICTED NORMAL
1. Lung Volumes in cc.			
Vital capacity			
Before epinephrine	1,594	2,082	2,715
After epinephrine	1,795	2,037	2,715
Residual air	1,197	696	829
Total capacity	2,791	2,778	3,544
$\frac{\text{Residual air}}{\text{Total capacity}}$ in per cent	42.9	25.1	23.4
2. Maximum Breathing Capacity in liters per minute			
Before epinephrine	25	36	78
After epinephrine	37	39	78
Ventilation in L/min/m² B.S.A.			
Basal	4.0	4.1	3.2
Leg exercise*	9.2	10.9	
Breathing reserve in per cent			
Basal	75	83	>92
Leg exercise*	43	52	—
3. Index of Intrapulmonary Mixing: Alveolar N_2 per cent	8.2	6.6	<2.5
Arterial Blood: Oxyhemoglobin saturation in per cent			
Basal	91.8	95.1	96
Leg exercise*	92.9	97.5	96
Oxygen tension in mm. of mercury	82	82	95
Carbon dioxide tension in mm. of mercury	45	39	40
4. Inspired-alveolar oxygen gradient in mm. of mercury	57	47	48
Alveolar-arterial oxygen gradient in mm. of mercury	9	19	<12
$\frac{\text{Venous admixture}}{\text{Total pulmonary blood flow}}$ in per cent	2.3	4.1	<6
5. Oxygen Consumption in cc/min/m² B.S.A.			
Basal	136	116	126
Leg exercise*	287	306	—

* A steady state of exercise achieved by a bicycling movement of the legs while lying supine during cardiac catheterization.

volume ratios, distribution of tidal air among the alveoli became more uniform. Underventilation of groups of alveoli was eliminated and the venous admixture to total pulmonary blood flow decreased to normal (figure 3).

In patient *L. M.* fairly extensive and clinically well-established sarcoidosis of the lungs was complicated by wheezing which responded to bronchodilators. As expected in this fibrotic condition of the lungs (16), the total lung volume was decreased. The presence of complicating emphysema was manifested by increased residual air volume and an RA/TC ratio greater than 35 per cent. Obstruction of the intrapulmonary airways was partially responsible in limiting vital capacity and MBC, as indicated by the increase in both tests after epinephrine (table 6 and figure 4).

Within three days on cortisone therapy, the patient noted subsidence of wheezing and cough; exertional dyspnea became less pronounced and the chest became clear on auscultation. Studies performed on the ninth, twelfth, and fourteenth days of hormone administration revealed no change in lung size. Vital capacity, however, had increased at the expense of the residual air, which now was less than the predicted value and occupied only 25.1 per cent of tota

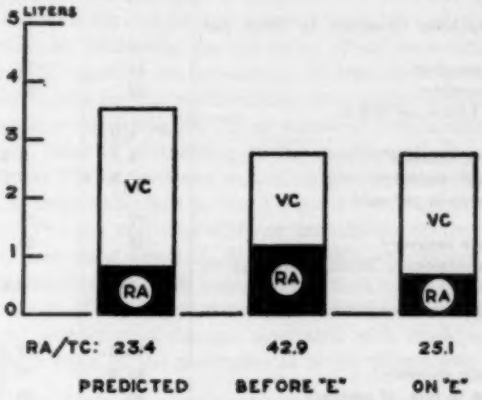

FIG. 4. Lung volumes in patient *L. M.* For symbols see figure 2.

capacity (figure 4). Aside from improvement in ventilatory capacity, the remainder of the changes were not thought to be significant. Judging from serial roentgenograms of the chest, the underlying fibrosis did not appear to be affected by cortisone.

Patient *J. McC.* had a long-standing history of bronchiectasis complicated by frequent pulmonary infections, emphysema, fibrosis, and cor pulmonale. Despite treatment with digitalis, low sodium diet, mercurials, bronchodilators, and intermittent phlebotomies, his course had been downhill. During ACTH administration there was subjective improvement in well being. Pulmonary signs cleared and the patient noted more effective and productive cough, followed by considerable relief of dyspnea.

Beneficial changes in function on the tenth and fourteenth days of ACTH administration included a small decrease in residual air volume and apparent

potentiation of response to Vaponefrin, as indicated by vital capacity and MBC measurements (table 7). Further depression of a very low arterial oxygen ten-

TABLE 7

Pulmonary Function Studies—Patient J. McC. (Male, 50 Years)

	BEFORE ACTH ADMINISTRATION	DURING ACTH ADMINISTRATION	PREDICTED NORMAL
1. Lung Volumes in cc.			
Vital capacity			
Before Vaponefrin	1,493	1,470	3,666
After Vaponefrin	1,810	1,916	3,666
Residual air	1,571	1,355	1,631
Total capacity	3,064	2,825	5,297
$\frac{\text{Residual air}}{\text{Total capacity}}$ in per cent	51.3	48.0	30.8
2. Maximum Breathing Capacity in liters per minute			
Before Vaponefrin	34	36	117
After Vaponefrin	42	53	117
Ventilation in L/min/m² B.S.A.			
Basal	4.0	4.1	3.9
1 minute leg exercise*	6.7	6.6	—
First minute recovery	7.8	6.7	—
Breathing reserve in per cent			
Basal	77	78	>92
First minute recovery	45	64	—
3. Index of Intrapulmonary Mixing: Alveolar N_2 per cent	5.9	5.6	<2.5
Arterial Blood: Oxyhemoglobin saturation in per cent			
Basal	78.5	73.0	96
First minute recovery	81.9	71.3	96
Oxygen tension in mm. of mercury	52	38	95
Carbon dioxide tension in mm. of mercury	65	62	40
4. Inspired-alveolar oxygen gradient in mm. of mercury	71	76	48
Alveolar-arterial oxygen gradient in mm. of mercury	26	35	<12
$\frac{\text{Dead space}}{\text{Tidal volume}}$ in per cent	41	41	<30
$\frac{\text{Venous admixture}}{\text{Total pulmonary blood flow}}$ in per cent	31	51	<6
5. Oxygen Consumption in cc/min/m² B.S.A.			
Basal	156	161	132
1 minute leg exercise*	181	190	—

* Bicycling movement of legs for one minute starting from rest while lying supine.

sion and oxyhemoglobin saturation, associated with an increase in the venous admixture to pulmonary blood flow, were undesirable effects of the hormone. They could not be attributed to fluid retention since the patient was main-

tained on a strict low sodium diet with limited fluid intake during hormone administration and did not gain weight. The development of interstitial edema of the alveoli, however, might well explain these changes.

COMMENT

That obstruction of the smaller intrapulmonary airways plays a role in the production of many of the cardinal physiologic defects of most cases of emphysema has long been appreciated. The pathogenesis of the anatomic changes in the lungs is currently believed to be due to bronchiolar obstruction (6, 7, 18). The use of bronchodilators has therefore been a rational part of the treatment of this disease.

ACTH and cortisone have produced changes in pulmonary function qualitatively similar to those achieved by nebulized Vaponefrin and subcutaneously administered epinephrine. The mode of action of cortisone and ACTH in accomplishing these effects is not certain, but it seems probable that they exert a bronchodilating action by decreasing the reactivity of the bronchiolar musculature to allergens and by causing the subsidence of chronic inflammatory changes in the bronchial mucosa similar to the subsidence of such changes in the diseased nasal and sinus mucosa during ACTH or cortisone administration (8, 9).

Quantitatively, relief of obstruction of the smaller radicals of the bronchial tree effected by ACTH or cortisone was much greater than that accomplished by conventional bronchodilators in the 2 patients with emphysema presented above in detail. The full and true effect of bronchiolar obstruction in limiting vital capacity, increasing residual air, restricting ventilatory capacity, and causing uneven distribution of air among the alveoli could be appreciated only during their courses of ACTH or cortisone. Loss of pulmonary elasticity and other permanent parenchymal changes associated with emphysema apparently played only minor roles in the pathogenesis of the pulmonary insufficiency in these patients.

In the patient with sarcoidosis complicated by obstructive emphysema, the alterations in function during cortisone administration were characterised by relief of bronchiolar obstruction and were therefore in the direction of the changes in the 2 patients mentioned above (patients *M. C.* and *J. K.*). The underlying fibrosis of this patient's lungs, which did not vary during treatment, presumably prevented further progress to normal. It is probable that maximal relief of bronchiolar obstruction was accomplished by cortisone.

The minimal responses to the hormones in those patients in whom bronchiolar obstruction did not exist strengthens the impression that ACTH and cortisone act in a general sense as bronchodilators. There is little reason, therefore, to expect that these agents will affect degenerative or senile emphysema of the variety that pre-hormone studies demonstrated to be present in patient *A. vU.* Moreover, it is anticipated that the efficacy of ACTH and cortisone will be limited in very advanced, longstanding types of obstructive emphysema with marked disturbance of gas exchange pattern. In these cases, pronounced anatomic changes in the nature of extensive alveolar destruction, reduction in the

area of alveolar-capillary interface available for gas exchange, and pulmonary arteriosclerosis will undoubtedly circumscribe the therapeutic response.

Patient *J. McC.* is a case in point. Although his response to Vaponefrin was potentiated while on ACTH, the remainder of his studies indicated further deterioration rather than improvement. Such diminution of pulmonary function in far advanced emphysema has been reported recently (17), and may be ascribed to the development of interstitial alveolar edema. The possibility of accentuating acutely pre-existing anoxemia by cortisone or ACTH in patients with severe and chronic restriction of pulmonary function, therefore, looms as a distinct therapeutic hazard.

SUMMARY

Pulmonary function was studied before and during administration of adrenocorticotropic hormone (ACTH) and cortisone in 9 patients with various types of chronic lung disease. Subjective and objective improvement, sometimes dramatic, occurred in those patients whose disease was secondary to or complicated by bronchiolar obstruction and was minimal or absent in those without obstruction. This observation, together with the pattern of change in pulmonary function, suggested that ACTH and cortisone exerted a sustained bronchodilating action. The effect of these agents on the bronchial tree was greater than the action of conventional bronchodilators in at least 2 patients with chronic obstructive emphysema, and was helpful in revealing the true extent to which their functional impairment could be attributed to bronchiolar obstruction rather than to permanent anatomic changes. Further depression of gas exchange encountered in a patient with cor pulmonale was thought to reflect the development of edema of the alveolar membrane. Such side effects are hazards of ACTH and cortisone administration in far advanced chronic lung disease.

SUMARIO

Algunos Efectos de ACTH y Cortisona sobre la Función Pulmonar en los Enfermos con Enfisema Oclusivo

En 9 enfermos con varias formas de neumopatía crónica, estudióse la función pulmonar antes de, y durante, la administración de ACTH y cortisona. En aquellos en que la enfermedad era secundaria a, o estaba complicada por, obstrucción bronquiolar y era mínima o nula en los que no tenían obstrucción, sobrevino mejoría subjetiva y objetiva a veces teatral. Esta observación, unida al patrón de la alteración de la función pulmonar, indicaba que ACTH y la cortisona ejercían una sostenida acción broncodilatadora. El efecto de dichos agentes sobre el árbol bronquial fué mayor que el de los habituales broncodilatadores por lo menos en 2 sujetos con enfisema oclusivo crónico y ayudó a revelar exactamente hasta qué punto cabía imputar la disfunción presente a oclusión bronquiolar más bien que a permanentes alteraciones anatómicas. Una nueva disminución del intercambio gaseoso en un enformo con cor pulmonale se consideró que reflejaba la aparición de edema de la membrana alveolar. Esos efectos subsidiarios constituyen riesgos que acompañan a la administración de ACTH y cortisona en las afecciones pulmonares crónicas y muy avanzadas.

RESUME

Certains effets de l'ACTH et de la cortisone sur la fonction pulmonaire de malade atteints d'emphysème par obstruction

La fonction pulmonaire a été étudiée chez 9 sujets atteints d'affections pulmonaires chroniques de types divers avant et après l'administration d'ACTH et de cortisone. Chez les malades dont les troubles étaient secondaires à l'obstruction bronchique, ou compliquée par elle, une amélioration objective ou subjective, parfois spectaculaire, s'est manifestée; ce phénomène était absent ou peu marqué dans les cas où l'obstruction n'existait pas. Cette observation, ainsi que les différents changements observés dans la fonction pulmonaire suggèrent que l'ACTH et la cortisone exercent une action dilatatrice soutenue sur les bronches. L'effet de ces médicaments sur les bronches s'est montré supérieur à celui des broncho-dilatateurs classiques dans au moins deux cas d'emphysème chronique par obstruction et ils ont servi à démontrer dans quelle mesure les troubles fonctionnels pouvaient être attribués à l'obstruction bronchique, plutôt qu'à des altérations anatomiques permanentes. Chez un malade atteint de dilatation du coeur droit, une diminution des échanges gazeux a paru refléter la présence d'oedème dans la membrane alvéolaire. De tels effets secondaires représentent les accidents déterminés par l'administration de l'ACTH et de la cortisone dans les affections chroniques du poumon à un stade avancé.

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THE EVOLUTION OF TUBERCULOUS LESIONS IN THE GUINEA PIG DURING ADMINISTRATION OF ADRENOCORTICOTROPIC HORMONE (ACTH) OR CORTISONE[1, 2]

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INTRODUCTION

Striking effects of cortisone administration upon the course of tuberculous infection have been reported in a number of investigations involving several animal species, including man (1–7). Interpretation of the nature of these effects has varied, and it appears that the influence of the hormone on tuberculous lesions may be significantly different in the different animal species. Lurie and his associates have demonstrated that experimentally infected rabbits of high genetic susceptibility to tuberculosis, when treated with cortisone, react with certain of the essential pathologic responses characteristic of natively resistant rabbits (1). In the genetically susceptible rabbit under the influence of cortisone, more pulmonary tubercles developed, but the size of the tubercles as well as their spread underwent reduction, caseation was greatly increased within the tubercles, and dissemination of microorganisms to the draining lymph nodes was much less than in litter mates which had received no cortisone. These are characteristics usually attributable to genetically resistant rabbits. A distinctive feature not generally observed in either resistant or susceptible rabbits was the presence of extraordinarily large numbers of acid-fast bacilli in the pulmonary lesions of animals treated with cortisone.

Spain and Molomut have reported the effects of cortisone upon the development of tuberculous lesions in guinea pigs experimentally infected two and four weeks prior to administration of the hormone (2). The tuberculous lesions appeared to be more extensive, more widely distributed, and individual lesions less well localized in the animals given cortisone. The subcutaneous nodules at the site of inoculation were more diffuse and incompletely encapsulated. Moreover, the draining lymph nodes in the animals given cortisone exhibited greater involvement with more caseous necrosis than the corresponding nodes of control animals.

In the albino rat, an animal natively resistant to progressive tuberculous disease, Michael and his associates have reported fulminating rapidly fatal tuberculosis when experimentally infected animals were treated with cortisone (3). A similar exacerbation of a chronic pulmonary infection in cortisone-treated mice

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has been reported by Hart and his associates (4). Solotorovsky and his associates have reported the suppression of an anticipated beneficial effect of vaccine in cortisone-treated mice although the rate of progression of the challenge infection was not obviously enhanced.

Information concerning the effects of adrenal steroids upon experimental tuberculosis has been limited to investigations in which cortisone was the sole agent used. Studies of the effects of adrenocorticotropic hormone (ACTH) upon the tuberculous process, however, have been conducted in humans (6, 7). In one of these studies (7), the alterations induced in the host-parasite relationship by the administration of ACTH were, for the most part, equally evident following the use of cortisone. It is worthy of reemphasis, however, that, despite many similarities in the metabolic effects of cortisone and ACTH, many differences in the effects produced by the two hormones have been recognized. The basis for one of the most significant differences between ACTH and cortisone may be related to the effect of these agents upon the function and size of the intact adrenal cortex. Whereas cortisone administration may suppress the production of steroid complexes by the adrenal cortex, the administration of ACTH results in increased activity of the gland. In some degree, therefore, the exhibition of differences between cortisone and ACTH may be anticipated to be dependent on the particular functions served by the normal adrenal gland in the animal species chosen for study. The necessary practice of utilizing several animal species to study hormone effects upon experimental tuberculous infections thus adds complexity to the problem of comparison of the two agents.

The present study was designed to investigate the effects of excessively large doses of ACTH and cortisone upon the initiation and early progression of a severe experimental tuberculous infection in the albino guinea pig. The character and extent of tuberculous involvement was examined in animals given ACTH and cortisone before and during infections of fourteen and twenty-eight days' duration.

Materials and Methods

Fourteen-day infection: Thirty male albino guinea pigs, weighing 250 to 350 gm., were divided into three equivalent groups. The number of animals per group and the dosage of the agents administered were as follows:

Group I. 10 animals—sterile sodium chloride (0.85 per cent NaCl), 0.2 cc. by the subcutaneous route every twelve hours.

Group II. 10 animals—cortisone acetate[4], 5 mg. subcutaneously every twelve hours.

Group III. 10 animals—adrenocorticotropic hormone (Armour Standard LA-1-A)[5], 8 mg. subcutaneously every eight hours.

Forty-eight hours after the initiation of hormone or saline administration, each animal in all groups was infected subcutaneously over the sternum with an inoculum of virulent microorganisms from a seven-day-old Tween[6]-albumin culture of *Mycobacterium tubercu-*

[4] The cortisone acetate used in this investigation was obtained through the courtesy of Dr. J. M. Carlisle, Merck & Company, Rahway, New Jersey.

[5] The adrenocorticotropic hormone used in this investigation was obtained through the courtesy of Dr. John Mote, Armour & Company, Chicago, Illinois.

[6] Tween 80 is the proprietary name of the polyoxyethylene derivative of Sorbitan monooleate, obtained from the Atlas Powder Co., Wilmington, Delaware.

losis (H37Rv). Each animal received in 0.5 ml. of Sorenson's phosphate buffer (pH 7.3) an amount of diluted culture equivalent to 0.0006 ml. of the original seven-day culture. (By turbidimetric measurement with reference to the previously established standard of this laboratory, it is estimated that each animal received approximately 50,000 viable units of tubercle bacilli.) Hormone or saline administration was continued for fourteen days, at which time all surviving animals were sacrified by a blow on the head. Palpation of the site of infection was intentionally avoided during the experiment.

Twenty-eight day infection: The experiment with the twenty-eight-day infection was designed essentially as was the fourteen-day infection with the exception of the dosage in the animals given ACTH. All male albino guinea pigs in this experiment weighed between 250 and 350 grams. The number of animals per group and the dosage of the agents administered were as follows:

Group I. 11 animals—sterile sodium chloride (0.85 per cent NaCl), 0.2 cc. subcutaneously every twelve hours.

Group II. 13 animals—cortisone acetate, 5 mg. subcutaneously every twelve hours.

Group III. (a) 8 animals—adrenocorticotropic hormone, 2.5 mg. subcutaneously every eight hours.

(b) 5 animals—adrenocorticotropic hormone, 8 mg. subcutaneously every eight hours.

Forty-eight hours after the initiation of hormone or saline administration, all animals were infected subcutaneously over the sternum with an infecting inoculum equivalent to that used in the infection of fourteen days' duration. The hormone or saline administration was continued for twenty-eight days, at which time all surviving animals were sacrificed by a blow on the head. Palpation of the site of infection was intentionally avoided during the experiment.

On the eighteenth day after infection, 5 animals from each of the three groups (*Groups I, II,* and *III b*) in the twenty-eight-day infection were selected for tuberculin testing. Each of the 15 animals was injected intracutaneously with 0.1 ml. of 0.5 per cent Old Tuberculin and the results were noted at forty-eight and ninety-six hours.

Animals excluded from analysis: In the infection of fourteen days' duration, one animal given saline died four days after infection and one animal given ACTH died three days after infection. In the infection of twenty-eight days' duration, one saline-treated animal died twelve hours after infection and one ACTH animal in *Group III* (a) died six days after infection. As the tuberculous process was not sufficiently advanced in these animals to permit evaluation, they are not included in the results of the experiment.

Results

FOURTEEN-DAY INFECTION

A comparison of the findings at necropsy in the various animal groups is presented diagrammatically in figures 2 and 3. (See figure 1 for key.)

Observations at the Site of Infection

Group I (Saline): In all of the 9 animals the formation of a spherical, soft nodule, consisting of a small central area of caseation necrosis[7] surrounded by a fibrous capsule, was noted. Histologic examination revealed severe central necrosis with large areas of homogeneous material in all of the 9 specimens.

Group II (Cortisone): Only 5 of the 10 animals had macroscopically visible nodules at the site of infection. The nodules were flat and indurated and caseation

[7] The term "caseation necrosis" as used in this report refers to macroscopically visible degeneration in which the tissues are transformed into a semi-solid, cheesy mass.

necrosis was present in the central portion of one nodule. Histologic examination showed severe central necrosis with large areas of homogeneous material in all of the five specimens.

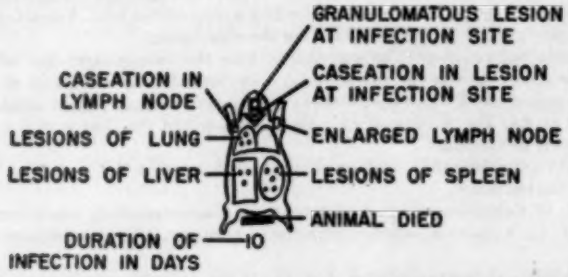

FIG. 1. Key to diagrammatic representation of nature and extent of tuberculous lesions (as modified by the authors from Feldman, W. H., and Hinshaw, H. C.: Chemotherapeutic testing in experimental tuberculosis, Am. Rev. Tuberc., 1945, *51*, 582.)

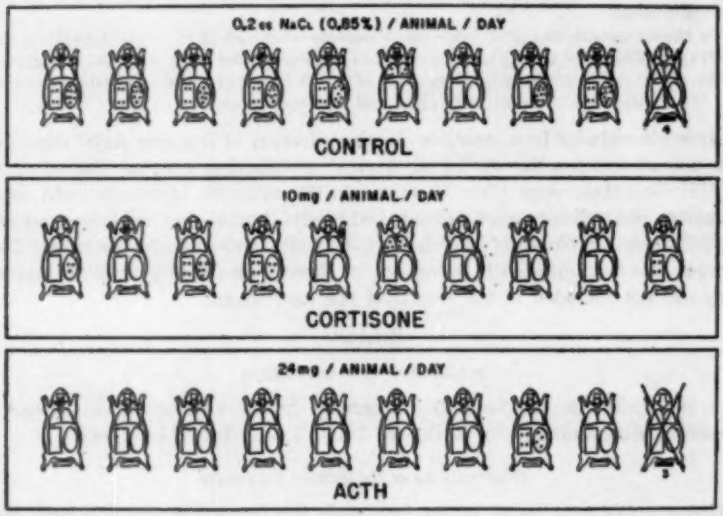

FIG. 2. Two-week infection. Gross pathologic changes noted on macroscopic examination

Group III (ACTH): In all of the 9 animals, the formation of a nodule at the site of infection was observed. The nodules were flat and indurated and one of the nine nodules contained a 3 mm. central area of caseation necrosis. Histologic

examination revealed severe central necrosis in all nine nodules, eight of which contained large areas of homogeneous material.

The nodules varied greatly in size from one animal to another but the greatest diameter of the nodules, when averaged, was approximately the same in all of the three groups. The width of the connective tissue capsule about the areas of necrosis in the nodules was approximately equal in all of the three groups when measured microscopically.

Acid-fast bacilli were numerous in all nodular formations. The microorganisms were equally abundant in all specimens.

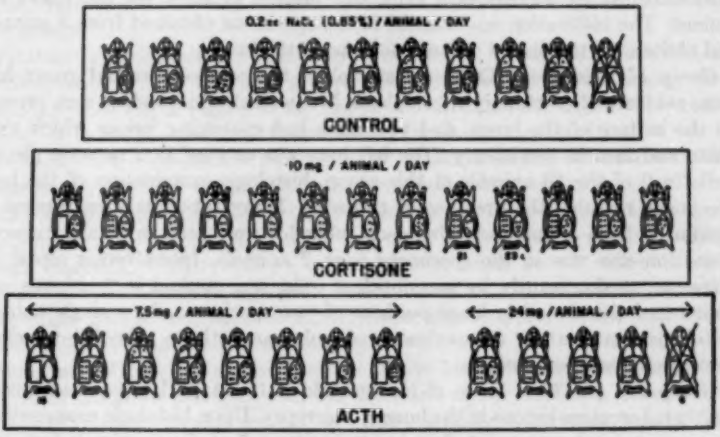

FIG. 3. Four-week infection. Gross pathologic changes noted on macroscopic examination

Observations on the Extent of the Tuberculous Lesions

Axillary Lymph Nodes

Group I (Saline): All of the 9 animals of this group had enlarged lymph nodes. Central caseation necrosis was noted in one node. Specimens from only 5 animals were available for histologic examination. In 4, the lymph nodes contained areas of necrosis with many tubercles present, and in one animal the node was hypertrophic, with early tubercle formation without extensive necrosis.

Group II (Cortisone): One animal of this group had an enlarged lymph node in which central caseation necrosis was present. Upon histologic examination of the specimens from other animals, 2 animals had lymph nodes in which moderate necrosis and many tubercles were noted, and one lymph node from another animal had early tubercle formation without extensive necrosis.

Group III (ACTH): One animal of this group had an enlarged lymph node which on histologic examination was seen to contain areas of moderate central

necrosis with many tubercles present. A lymph node from another animal revealed early tubercle formation without extensive necrosis.

Lungs

Group I (Saline): Only one animal had gross evidence of pulmonary tuberculosis. The lower lobes of the lungs had small coalescing lesions which were white and firm in consistency. Small tubercles were present over the other lobes. In all of the 8 animals, histologic examination revealed the presence of tubercles. In 2 animals, many tubercles were present; tubercle formation was infrequent in 4; and rare in the specimens from 2 animals. Interalveolar septal infiltration, predominantly by mononuclear cells, was present in all of the specimens examined. The infiltration was marked in the specimens obtained from 3 animals and obliterated the alveoli of large portions of the lung.

Group II (Cortisone): Only one animal in the cortisone-treated group had gross evidence of pulmonary tuberculosis. Many small white lesions were present on the surface of the lungs, and two lobes had coalescing lesions which were white and firm in consistency. The left lung was encased in a necrotic pleural wall. In 9 of the 10 animals of this group, histologic examination of the lung specimens revealed the presence of tubercles. Many tubercles were present in specimens from 4 animals; infrequent tubercles were seen in 3, and tubercle formation was rare in the specimens from 2 animals. Interalveolar septal infiltration, predominantly by mononuclear cells, was marked in 4 animals and obliterated the alveoli in large portions of two specimens. In a single animal, histologic examination of specimens of pulmonary tissue revealed no characteristic tuberculous lesions.

Group III (ACTH): None of the animals in the ACTH group had grossly visible tuberculous lesions in the lungs at necropsy. Upon histologic examination, however, tubercles were noted in specimens from 5 of the 9 animals but were rare in all instances. Slight infiltration of the interalveolar septa by mononuclear cells was present in specimens from 7 animals, and the specimen from one animal was essentially normal.

Acid-fast bacilli were equally difficult to find in all specimens. No evidence of pseudotuberculosis was obtained (8).

Liver

Group I (Saline): Six of the 9 animals had small white lesions on the liver surface. All of the 9 animals had small tubercles present in the liver on histologic examination. Many tubercles were present in the specimens from 5 animals, and tubercle formation was infrequent in the other 4 animals.

Group II (Cortisone): Three animals had small white lesions on the surface of the liver. Upon histologic examination, small tubercles were present in specimens from 5 of the 10 animals. Many tubercles were present in one animal, infrequent tubercles were present in another, and tubercle formation was rare in specimens from 3 animals. The livers of the remaining 5 animals were normal.

Group III (ACTH): One animal had small white lesions on the liver surface. In 7 of the 9 animals, small tubercles were seen on histologic examination. Many

tubercles were observed in one specimen and tubercle formation was rare in 6 specimens. The hepatic tissues from 2 animals were essentially normal.

Acid-fast bacilli were present in many of the hepatic tubercles in the animals of all of the three groups and no difference was demonstrable among the groups in the number of acid-fast bacilli in each tubercle.

Spleen

Small tubercles were present on the spleen of 7 of the animals which received saline. Three of the animals which received cortisone had small tubercles present on the spleen, as did one animal in the group which received ACTH. No significant difference in the size of the spleen was observed in the animals of the three groups.

Histologic examination showed many tubercles to be present in all of the splenic specimens from all three groups. No significant difference among the groups was observed in regard to the size of the tubercles, the degree of necrosis present, or in the number of acid-fast bacilli present in the tubercles.

Comment: In the infection of fourteen days' duration, certain differences in the character and extent of the tuberculous process were observed upon comparison of the findings at necropsy of the three animal groups. The nodules at the site of infection in the saline-treated animals were more spherical and contained more caseous material. Axillary lymph nodes were enlarged in all saline-treated animals but lymph node enlargement was observed in only one animal in each of the other groups. The saline-treated animals also had more numerous small lesions of the liver and spleen at necropsy.

The extent of tuberculous involvement of the lungs was approximately the same in all groups at necropsy with the exception of one animal in each of the saline- and cortisone-treated groups. In these 2 animals, pulmonary lesions, far advanced for an infection of such short duration, were evident at necropsy. Attempts to demonstrate the presence of microorganisms other than *Mycobacteria* (8) in these animals were unsuccessful.

It is noteworthy that nodules at the infection site formed in all ACTH-treated animals, whereas the formation of a nodule was observed in only one-half of the animals given cortisone.

TWENTY-EIGHT DAY INFECTION

A comparison of the findings at necropsy in the three groups of animals is presented diagrammatically in figure 3.

One animal given ACTH (*Group IIIb*) died on the eighteenth day after infection. Two animals given cortisone died before completion of the experiment, one on the twenty-first day after infection and the other on the twenty-third day after infection. The findings in these animals are included below.

Observations at the Site of Infection

In all animals in all groups a nodule formed at the site of initial infection. Ulceration and drainage through the skin at the site of infection were observed in

3 animals given saline, in one animal given cortisone, and in 4 animals given the smaller dose of ACTH (*Group IIIa*).

The maximum diameter of the intact nodules was measured and averaged. The nodules in the group of animals which received the smaller dosages of ACTH averaged 1.5 cm. in diameter; those in the group given the larger dosage of ACTH, 1.6 cm. in diameter; those in the group given cortisone, 1.2 cm. in diameter; and those in the group given saline averaged 1.2 cm. in diameter.

As no significant difference was noted at necropsy between the two animal groups receiving ACTH, except as presented above, they will be reported as a single group.

Group I (Saline): Seven of the 10 animals had intact nodules at the inoculation site. The nodules were spherical, soft, and consisted of a large area of central caseation necrosis surrounded by a thin fibrous capsule. The caseation necrosis was greater in amount than that seen in the animals which received ACTH or cortisone.

Group II (Cortisone): Twelve of the 13 animals had intact nodules at the site of inoculation. The nodules were less spherical than in the saline controls, were soft, and consisted of an area of central caseation necrosis of varied size surrounded by a fibrous capsule. The nodules were comparable to those seen in the animals receiving ACTH.

Group III (ACTH): Eight of the 12 animals had an intact nodule at the site of inoculation. The eight nodules were less spherical than in the saline controls, were soft, and consisted of an area of central caseation necrosis of varied size surrounded by a fibrous capsule.

Histologic examination of the intact nodules from all groups revealed severe central necrosis containing large areas of homogeneous debris. The fibrotic reaction about the areas of necrosis in the nodules was similar in extent in all specimens. Acid-fast bacilli were numerous in all nodules and the microorganisms were equally abundant in all specimens from all groups of animals.

Observations on the Extent of the Tuberculous Lesions

Axillary Lymph Nodes

Group I (Saline): Eight of the 10 animals had enlarged axillary lymph nodes, six of which had central caseation necrosis. Six of the eight enlarged nodes had severe central necrosis with many tubercles noted on histologic examination, and, in another, tubercles were present. In another animal many tubercles were present in a lymph node which had not been noted to be enlarged at necropsy. Acid-fast bacilli were present in all specimens examined.

Group II (Cortisone): Ten of the 13 animals had enlarged axillary lymph nodes, three of which had central caseation necrosis. Upon histologic examination, eight of the ten enlarged nodes had severe central necrosis, and the other two had moderate central necrosis. In addition, 2 animals had histologic evidence of tuberculous involvement of lymph nodes which had not been appreciably enlarged at necropsy. The lymph nodes from both of these animals contained tubercles,

and early central necrosis was present in one. Acid-fast bacilli were present in all nodes examined.

Group III (ACTH): Eight of the 12 animals had enlarged axillary lymph nodes, two of which had central caseation necrosis. Upon histologic examination, six of the eight enlarged nodes revealed severe central necrosis, moderate central necrosis was present in one, and, in the other, several tubercles were present. Acid-fast bacilli were present in all lymph nodes examined.

Lungs

Group I (Saline): Six of the 10 animals had grossly visible pulmonary lesions. Histologic examination revealed tubercles to be present in the lungs of all animals. Many tubercles were noted in the lungs of 8 animals and several tubercles were present in the lungs of 2 animals.

Group II (Cortisone): Only 3 of the 13 animals had grossly visible pulmonary lesions. Histologic examination revealed tubercles to be present in the lungs of 12 of the 13 animals. Many tubercles were noted in the lungs of one animal, several tubercles in the lungs of 10 animals, and rare tubercles in the lungs of one animal. Interstitial infiltration by mononuclear cells was noted in the lungs of all animals and was extreme in portions of the specimens from 7 animals.

Group III (ACTH): Four of the 12 animals had grossly visible pulmonary lesions. Histologic examination revealed tubercles in the lungs of 10 animals. Many tubercles were noted in the lungs of one animal, several tubercles in the lungs of 6, and rare tubercles in the lungs of one animal. The specimen in which many tubercles were found was from the animal which died on the eighteenth day after infection. All of the 12 animals had interstitial infiltration by mononuclear cells and the process was extreme in portions of the specimens from 6 animals.

Acid-fast bacilli were sparsely present in all lung specimens and were equally difficult to find in all specimens.

Liver

Group I (Saline): Seven of the 10 surviving animals had definite hepatic lesions on macroscopic examination. Histologic examination of the available specimens (9 animals) revealed tubercles to be present in all. Many tubercles were present in the livers of 7 animals, and infrequent tubercles were present in the specimens from 2 animals.

Group II (Cortisone): Six of the 13 animals had definite hepatic lesions on macroscopic examination. Histologic examination revealed tubercles in all of the 13 animals. Many tubercles were noted in the liver of one animal and infrequent tubercles were present in the specimens from the other 12 animals.

Group III (ACTH): Eight of the 12 animals had definite hepatic lesions on macroscopic examination. Histologic examination revealed tubercles in the specimens from all of the 12 animals. Many tubercles were present in the livers of 3 animals and infrequent tubercles were noted in the specimens from the other 9 animals.

Acid-fast bacilli were present in all specimens examined from the animals in all three groups.

Spleen

Ten of the 12 animals in the group which received ACTH had grossly visible lesions of the spleen. All of the animals given cortisone and all of the animals given saline also had grossly visible lesions of the spleen. The size of the spleen was greatest in the group of animals which received saline, and the lesions were more obvious. The spleen was smallest in the animals given cortisone.

Histologic examination of the spleen showed many tubercles present in all specimens. No significant differences in the tuberculous process among the groups was noted on microscopic examination. The lymphocytic components of the spleen were least, and the fibrotic stroma most, prominent in the animals which received cortisone.

Tuberculin Hypersensitivity

The saline-treated animals which were tested for cutaneous hypersensitivity to tuberculoprotein exhibited a markedly positive reaction on the twentieth day after infection. The animals given cortisone or ACTH developed an equivocal reaction at the site of the test characterized by slight erythema and an area of induration less than 5 mm. in diameter.

Comment: In the infection of twenty-eight days' duration, the character and extent of the tuberculous process was more uniform among the three groups than in the fourteen-day infection. Observations of the character of the tuberculous process at the site of inoculation revealed no major differences in the nodular lesions except that caseation necrosis was more evident in the saline-treated animals. It is worthy of emphasis that all of the cortisone-treated animals had nodules at the site of infection which were similar in size and consistency to those in the ACTH-treated animals. Significant differences in the extent of the tuberculous process among the animal groups were not observed.

Ulceration and drainage through the skin of the site of infection were noted in 3 saline-treated animals, in one cortisone-treated animal, and in 4 animals given the smaller ACTH dosage (*Group IIIa*). The skin at the site of infection was intact in all of the animals which received the larger ACTH dosage (*Group IIIb*).

Discussion

In the present investigation, excessively large amounts of cortisone and ACTH were administered to guinea pigs before and during a very severe experimental tuberculous infection in an attempt to increase the magnitude of the effects of these hormones upon the initiation and early progression of the tuberculous process.

The effects induced by ACTH and cortisone were most evident in the experimental infection of fourteen days' duration. In both groups of animals which received the hormones, the characteristics of the nodule at the inoculation site were definitely altered. Formation of such a nodule at the inoculation site was

noted, however, in only one-half of the cortisone-treated animals, whereas a nodule formed in all of the animals which received ACTH. Demonstrable involvement of the various organs by the tuberculous process was less frequent in the animals given cortisone or ACTH than in the control animals which received only saline.

The effects induced by ACTH or cortisone were not as pronounced in the experimental infection of twenty-eight days' duration. In the longer experiment the formation of a nodule containing caseation necrosis occurred in all animals irrespective of the substance administered. The extent of the tuberculous process in all groups of animals was approximately the same. Significant differences among the three groups in terms of the number of acid-fast bacilli present in the lesions were not demonstrable on microscopic examination of the tissues.

The present study was designed to investigate only a limited aspect of the effects of these hormones upon an experimental tuberculous process. Variations in the extent of the tuberculous process occurred in the individual members of each animal group irrespective of the agent administered. Nevertheless, evidence of enhancement of the experimental tuberculous process induced by cortisone or ACTH was not obtained during the period in which the excessively large amounts of these agents were administered.

Summary

An investigation of the effects induced by the administration of excessively large amounts of adrenocorticotropic hormone (ACTH) or cortisone upon the initiation and early progression of a very severe experimental tuberculous infection in the albino guinea pig has been described.

With both hormones, alterations in the evolution of lesions at the inoculation site and in the extent of the tuberculous process in other tissues were demonstrable in a fourteen-day experiment but were not evident in an experiment in which hormone administration was continued for twenty-eight days.

During the periods in which excessively large amounts of these hormones were administered, evidence of enhancement of the experimental tuberculous process was not obtained.

Sumario

La Evolución de las Lesiones Tuberculosas en el Cobayo Durante la Administración de Hormona Adrenocorticotropa (ACTH) o Cortisona

Descríbese el resultado de una investigación de los efectos evocados por la administración de cantidades excesivas de hormona adrenocorticotropa (ACTH) o cortisona sobre la iniciación y agravación temprana de un grave proceso tuberculoso experimental en el cobayo albino.

Con ambas hormonas, pudieron observarse alteraciones en la frecuencia de las lesiones en el sitio de inoculación, en las características de las lesiones y en la extensión del proceso tuberculoso, en un experimento que duró catorce días, pero no en otro en que se administraron las hormonas durante veintiocho días.

Durante los períodos de tiempo en que se administraron cantidades excesivas de dichos agentes, no se notaron signos de realce del proceso tuberculoso experimental.

Resume

Evolution des lésions tuberculeuses chez le cobaye au cours de l'administration de l'hormone corticotrope (ACTH) ou de la cortisone

Description d'une enquête sur les effets déterminés par l'administration de doses extrêmement élevées d'hormone corticotrope (ACTH) ou de cortisone sur le début ou l'évolution précoce d'un processus tuberculeux sévère, produit expérimentalement chez le cobaye.

Quand les deux hormones étaient administrées simultanément, des différences dans la fréquence des lésions au point d'inoculation, dans le caractère de ces lésions, et dans l'étendue du processus tuberculeux, ont du être observées dans les études expérimentales d'une durée de quatorze jours, mais non dans celles où les hormones ont été administrées pendant vingt-huit jours.

Pendant les périodes où les hormones étaient administrées à dose très élevée, l'exagération du processus tuberculeux n'a pu être démontrée.

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THE DISAPPEARANCE OF TUBERCLE BACILLI FROM THE SPUTUM FOLLOWING THORACOPLASTY[1]

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INTRODUCTION

In the majority of tuberculous patients, sputum cultures do not become negative for tubercle bacilli immediately upon completion of thoracoplasty. If positive cultures persist following thoracoplasty and a demonstrable source of "positive" sputum cannot be found in the bronchi or in any collapsed or uncollapsed portion of the lungs after adequate investigation, one is often forced to conclude that the tubercle bacilli are being discharged from unhealed lesions under the thoracoplasty. It is well recognized that this type of collapse frequently conceals cavities or lesions from detection by any present method of examination, including planigrams. Because resection under thoracoplasty is now done frequently under these circumstances, the writers believe that it is important to know the general rate of sputum "conversion" in a group of successful thoracoplasties, i.e., a group of patients in whom "conversion" is presumably a direct result of the thoracoplasty collapse.

During the past ten years the *Index Medicus* has listed very few articles (under "sputum, conversion of" and "thoracoplasty") which deal directly with this subject. Only Steele's study (1), based upon 43 thoracoplasties and 14 extrapleural pneumonolyses, clearly excludes all factors such as contralateral activity of tuberculous lesions, inadequate follow-up observations, tuberculous bronchitis, residual cavity, empyema, and bronchiectasis, any of which might affect the rate of conversion. Since Steele was primarily interested in analyzing other factors, however, he did not report the general cumulative rate of sputum "conversion" per month for his thoracoplasties alone. Other articles (2, 3, 4) have included consecutive thoracoplasties rather than only successful ones, or have not used sputum cultures as the basis for determining "conversion." For these reasons, it seems of interest to report a study of the rapidity of sputum "conversion" in 102 patients who received successful thoracoplasties.

PLAN OF STUDY

Selection of Cases

The thoracoplasties included in this study were performed on the service of Dr. John Alexander at the University Hospital, Ann Arbor, Michigan, using his technique (5). The patients were returned to the Michigan State Sanatorium for continuation of strict bed rest (for a minimum period of six months) and observation as soon as their postoperative condition permitted. The postoperative period was considered to begin on the date of completion of the last stage of thoracoplasty.

[1] From the Michigan State Sanatorium, Howell, Michigan.

A case was included in this series only if sufficient data could be obtained from the records and roentgenograms to fulfill the requirements of the 1950 National Tuberculosis Association classification of an "inactive" lesion or lesions. These requirements specify that all lesions must be stable, as observed on serial roentgenograms, and at least three specimens of sputum or gastric contents be negative for *M. tuberculosis* by culture, and that such conditions must have existed for six months or longer. In the majority of cases in the present study, sputum cultures were obtained routinely at monthly intervals. Cultures of gastric contents were made in most of the cases but in many instances were not done sufficiently frequently to make it possible to consider them separately in this study. Gastric cultures are, therefore, considered as sputum cultures. All

TABLE 1

The Intensity with Which Patients Were Followed Post Thoracoplasty with Sputum and/or Gastric Cultures

(Number of Post-Thoracoplasty Cultures (Grouped))

Number of cultures	4–6	7–10	11–15	16–20	21–25	26–30	31–37
Number of patients	6	18	24	25	16	7	6

TABLE 2

The Duration of the State of "Negative Cultures" in Months in 102 Cases of Successful Thoracoplasty

(Months of Consecutive "Negative Cultures")

Number of months	6–11	12–20	21–30	31–40	41–50	51–60	61–70	71–80	81–90	91–100	100–129
Number of patients	15	28	12	11	7	8	4	3	1	6	7

sputum was concentrated by a sodium hydroxide digestion method and inoculated on Petragnani's medium. Recently a precipitation-digestion method has been used. Two tubes of medium were inoculated for each culture and examined weekly. The cultures were discarded as negative for *M. tuberculosis* after eight weeks if they failed to show growth.

A patient was included in the series only if he or she had had four or more consecutive sputum or gastric cultures which were negative for *M. tuberculosis* during a period of six months or longer at some time following thoracoplasty and without additional therapy other than bed rest. The time of sputum "conversion" was considered to be the postoperative month in which the first negative culture of such a series occurred. If at any time following such a series of negative cultures one or more subsequent cultures were reported as positive for *M. tuberculosis*, the patient's case was discarded as not representing sputum "conversion." In table 1 it is shown that all except 6 of the patients had seven or more cultures during the postoperative period. An examination of table 2 reveals that the postoperative observation period was one year or longer in 87 of the 102 patients.

From the cases which satisfied the above requirements, additional ones were eliminated in which any of the following factors might confuse the results:

1. Several cultures were negative for *M. tuberculosis* just prior to thoracoplasty.
2. Contralateral active tuberculosis was present.
3. Active tuberculous endobronchitis was found following thoracoplasty.
4. Known bronchiectasis was present.
5. Thoracoplasty was performed for empyema or bronchopleural fistula.
6. Sputum cultures were not obtained sufficiently frequently during the first few postoperative months to determine accurately the time of "conversion."
7. Additional treatment of any kind other than bed rest was given following thoracoplasty.

From a total of approximately 400 cases reviewed, it was possible to collect 102 cases satisfying all of the above requirements and providing adequate data for study. Before operation, 77 patients were discharging tubercle bacilli as determined by microscopic examination of single or concentrated specimens of sputum; 15 patients were consistently positive by culture; and 10 patients were intermittently positive by culture but more frequently positive than negative.

TABLE 3

The Rate of Reversal of Infectiousness in 102 Cases of Uncomplicated Thoracoplasty

(Sputum "Conversion" Rate (Per Cent))

Postoperative month	1	2	3	4	5	6	7	8	9	10	11	12	14	16	19	24
Per cent converted each month	35	6	12	15	4	3	11	2	1	3	3	1	1	1	1	1
Cumulative rate	35	41	53	68	72	75	86	88	89	92	95	96	97	98	99	100
Average rate per month	12 per cent per month							2 per cent per month				0.4 per cent per month				

RESULTS

The percentage of patients becoming "culture negative" in each postoperative month as well as the cumulative percentage of "conversions" by months are shown in table 3. It will be noted that the percentage of cases with "conversion" decreased abruptly after the seventh postoperative month and that a further decrease occurred after the eleventh postoperative month. Calculation of the average "conversion" rate per month for these periods yielded a rate of 12 per cent per month for the first seven postoperative months, 2 per cent per month for the subsequent four months, and only 0.4 per cent per month during the following year.

Age of patient, size and number of cavities, and presence of bronchial involvement: An analysis of certain other factors shows that the age of the patient, the number and size of the cavities, thickness of cavity wall (as seen on the preoperative roentgenogram), and obvious inflation characteristics had no effect on the rate of sputum "conversion." Only 4 patients with immediately pre-

thoracoplasty roentgenographic evidence of so-called "blocked cavity" are included in this series and all "converted" immediately. Thirty-five patients had tuberculous bronchitis at some time preoperatively, but healing had occurred in all of these cases at the time of operation. There was no difference in the rapidity of "conversion" when the data from these patients were compared with those obtained from patients who had never had a known tuberculous bronchitis. Ten patients received streptomycin during the surgical period, but none received it therapeutically following operation. The number of patients who received streptomycin was too small to evaluate the effect of the drug on the rapidity of "conversion." The effect of duration of cavity on the rate of "conversion" could not be determined because most cavities were already present when the first roentgenograms were obtained.

TABLE 4

Correlation Between the Degree of Positivity of Sputum Immediately Before Thoracoplasty and the Rate of Sputum Conversion Following Thoracoplasty in 108 Patients with Uncomplicated Thoracoplasty

(Cumulative Rate of "Conversion" (Per Cent) with Respect to the Type of Laboratory Test Necessary to Demonstrate Bacilli Immediately Before Thoracoplasty)

TYPE OF LABORATORY TEST	NUMBER OF PATIENTS	POSTOPERATIVE MONTH							
		1	2	3	4	7	10	16	24
Smear-positive	68	22	28	38	57	82	90	97	100
Concentrate-positive	9	44	55	66	77		88	100	
Consistently culture-positive	15	66		79	92	100			
Intermittently culture-positive	10	70	80	100					

TABLE 5

Correlation Between the Type of Pericavitary Infiltration Immediately Before Thoracoplasty and the Rate of Sputum "Conversion" Following Thoracoplasty in 102 Cases of Successful Thoracoplasty

(Cumulative Rate of Sputum "Conversion" (Per Cent) with Respect to the Type of Pericavitary Infiltration)

POSTOPERATIVE MONTH	1	4	7	11
Fibrotic	65	76	100	
Mixed	32	73	90	97
Exudative	26	52	74	91

The only factors in this series which appeared to have any effect on the rapidity of sputum "conversion" were the character of the pericavitary infiltration existing at the time of thoracoplasty and the method of laboratory examination necessary to demonstrate tubercle bacilli just prior to thoracoplasty. In table 4 is shown the cumulative "conversion" rate with respect to the type of laboratory procedure necessary to demonstrate tubercle bacilli just prior to thoracoplasty. The figures reveal a definite lag in "conversion" rate for those patients

who were positive on microscopic examination just before thoracoplasty. This differs from Steele's (1) study in that he found that the "degree of positivity" of sputum immediately before operation had no effect on the rate of "conversion" following surgery. In table 5 it is shown that the presence of exudative infiltration definitely delays "conversion", a conclusion also reached by Steele (1).

COMMENT

It would seem that after the seventh post-thoracoplasty month the probability of spontaneous "conversion" of sputum is small, since "conversion" had occurred in 86 per cent of the cases of the present series by that time. The possibility of "conversion" one year after operation is almost insignificant. It must be remembered that these figures are from a highly selected series of successful thoracoplasties. In the consideration of any individual case, in which the degree of success of the thoracoplasty is not yet known, the percentage chance of spontaneous "conversion" during these periods is probably less than indicated here. Such figures cannot be applied in any arbitrary manner in deciding when to institute additional treatment, such as resection. Nevertheless, the figures obtained in the present study represent one of the many factors which must be considered in reaching a decision concerning excisional and other forms of therapy following thoracoplasty.

SUMMARY

From a group of approximately 400 thoracoplasty patients, it was possible to compile a selected group of 102 cases in which sputum "conversion" resulted directly from the thoracoplasty and in which adequate data were available for a study of the rate of sputum conversion following thoracoplasty.

It was found that "conversion" of sputum occurred in 86 per cent of patients during the first seven postoperative months (a rate of 12 per cent per month) and in an additional 10 per cent by the eleventh postoperative month (a rate of 2 per cent per month). The remaining 4 per cent of the patients "converted" during the following year at a rate of approximately 0.4 per cent per month.

Among the factors analyzed, the only ones which significantly delayed "conversion" were the presence of exudative pericavernous infiltration just before operation and "the degree of positivity" of sputum prior to thoracoplasty as indicated by the type of laboratory test necessary to demonstrate tubercle bacilli.

SUMARIO

Viraje del Esputo Consecutivo a la Toracoplastia

En una serie de 102 enfermos en los que la toracoplastia produjo viraje del esputo, se estudió la rapidez con que tuvo lugar el mismo.

Descubriése que el viraje del esputo sobrevino en 86 por ciento de los enfermos durante los primeros siete meses postoperatorios (una proporción de 12 por ciento al mes) y en otro 10 por ciento para el undécimo mes postoperatorio (una pro-

porción de 2 por ciento al mes). El restante 4 por ciento de los enfermos viraron durante el año siguiente a razón aproximadamente de 0.4 por ciento al mes.

Entre los factores analizados, los únicos que demoraron tangiblemente el viraje fueron la presencia de infiltración pericavernosa exudativa precisamente antes de la intervención y el grado de positividad del esputo antes de la toracoplastia según la clase de prueba de laboratorio necesaria para descubrir bacilos tuberculosos.

RESUME

Modification des crachats à la suite de la thoracoplastie

Dans une série de 102 malades où la thoracoplastie a été suivie d'une modification de l'expectoration, la rapidité de ce phénomène a été étudié.

On a trouvé que les modifications observées dans les crachats se produisaient dans 86% des cas, après l'intervention, pendant les sept premiers mois consécutifs a la thoracoplastie (soit une moyenne de 12% par mois; dans 10% des cas entre le septième et le onzième mois (soit 2% par mois). Chez les derniers 4% de ces malades le changement s'est effectué au cours de l'année suivante au rythme d'environ 0,4% par mois.

Parmi les facteurs analysés, les seuls qui retardent cette transformation sont: la présence d'infiltrations exudatives pericavitaires immédiatement avant l'opération et le degré de positivité du crachat avant la thoracoplastie, comme le montrent les différents tests de laboratoire nécessaire permettant d'identifier le bacille tuberculeux.

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Editorial

Mass Roentgenographic Surveys in Small Hospitals

When mass roentgenographic procedures were first applied on a wide scale to the tuberculosis case-finding program a few years ago, it was soon realized that the patients admitted to general hospitals constituted a large and readily accessible group on which the technique could be effectively used. It was further found that the yield of positive cases was considerably greater than that occurring in mass surveys of industrial populations and other groups. Hodges, one of the foremost pioneers in the application of routine photofluorographic procedures to the admissions of general hospitals, demonstrated that the incidence of tuberculosis among the patients admitted to the University of Michigan Hospital was 2.3 per cent. Moreover, the detection of such other pathology as cardiac enlargement, mediastinal tumors, and pulmonary neoplasms brought the total yield of significant lesions to almost 10 per cent. Thus, mass roentgenographic techniques in general hospitals are not only useful from the standpoint of tuberculosis case finding; they are also extremely valuable in the detection of a host of other pulmonary and vascular lesions which like tuberculosis are often unsuspected before the photofluorographic films are made.

Although the value of mass roentgenographic procedures in general hospitals is now undisputed, and although many of the larger hospitals throughout the United States are routinely obtaining chest roentgenograms of all patients admitted to their wards, there has been a rather slow acceptance of the method among hospitals having capacities of 50 to 250 beds. This has been due, in part, to the understandable reticence of attending radiologists to embark upon service programs which impose upon them an extra professional burden of not inconsiderable magnitude and which do not provide a reasonable return for their efforts. Many of the radiologists in the larger teaching hospitals who have used the material from their photofluorographic installations for the education of their radiologic residents have adopted a policy of providing routine small-film examinations at no cost to the patient. This procedure has caused health authorities in some quarters to advocate that routine chest examinations in all hospitals be given free of charge. Indeed, there are a few who find any other system quite unacceptable. This thinking, however, is not necessarily sound when applied to small hospitals.

In many small hospitals, funds are not available to furnish a mass photofluorographic installation from operating revenues, and accordingly the radiologist himself may be called upon to provide the necessary equipment. If this is the case, a no-charge policy for routine admission chest films can hardly be insisted upon. An outlay of ten to twelve thousand dollars will be required to complete the installation and, as we shall see presently, a charge of 75 cents to $1.50 per chest film will be necessary if this expense, together with associated budgets

for supplies and personnel, is to be balanced. Nevertheless, it should be recognized that a charge of approximately one dollar for a miniature chest film is a very reasonable levy for value received. Although these films can be regarded as no more than screening examinations of the chest, the frequent detection of unsuspected pathology makes them worth many times their cost to the persons with pulmonary lesions. Thus, where public funds are not available to install a routine chest unit in a small hospital, efforts to provide such a unit should not be abandoned; instead a program should be instituted whereby each patient is charged a nominal sum for the unit's support. Christmas Seal money could and should be used to pay for those persons who are unable to afford even a small charge. Indeed every community Tuberculosis Association should examine its budget very closely to determine how much money can be made available to demonstrate the value of the procedure by helping in the mass radiographic installations which are already in operation or which are being contemplated. In the latter case, there will be many instances where a little support from Christmas Seal funds will make successful mass chest survey programs in small hospitals.

Another reason for the slow acceptance of routine photofluorographic examinations in small general hospitals has been the belief that these procedures become inefficient and costly when numbers less than fifty to one hundred are to be examined each day. This, however, is far from the case. To illustrate this point let us first examine the situation in a large general hospital and then project our thinking into a hospital having a capacity of 100 beds.

The technical cost of performing a photofluorographic examination may be divided into the following categories:

a) Amortization on capital equipment
b) Service to capital equipment
c) Photofluorographic supplies such as film and developer
d) Personnel, including technician, secretary, and such other persons as are necessary
e) Rental of floor space
f) Utilities, including light, heat, telephone, and laundry.

In a large hospital, where the number of examinations performed each year may approach 15,000, the capital equipment which is needed includes a fully automatic photofluorographic unit costing, with darkroom accessories, approximately $12,000. This equipment can usually be operated over a ten-year period and accordingly an amortization rate of $1,200 per year should be established. The service charges to maintain this equipment in an operating state usually average five cents per exposure or $750 for 15,000 examinations. These charges will be incurred when X-ray tubes, valve tubes, or other components require replacement from time to time. The cost of photofluorographic film, developing chemicals, and other supplies for units using 70 mm. film also amounts to approximately five cents per exposure or $750 for 15,000 examinations.

The personnel needs of a photofluorographic installation will vary somewhat from one hospital to another. However, at the Johns Hopkins Hospital where the

yearly number of examinations approaches that in this example, one X-ray technician with an annual salary of $2,400 and one clerk-typist with an annual salary of $2,100 are needed. These individuals register the patients at the photofluorographic unit, make and process the films, take down the reports from the radiologists who read the films, and finally file the films and reports in the patients' histories. Both are kept busy throughout the entire working day.

The floor space needed for a photofluorographic installation usually approaches 500 square feet. At a nominal rental of three dollars per square foot per annum, such space represents an expense to the mass roentgenographic procedure of $1,500. The cost of utilities will be small if the patients are examined with their clothes on since this procedure avoids laundry expense. Electric power and telephone service may be expected to approach $300.

In summary then the technical cost of operating a photofluorographic unit in a large general hospital may be listed as:

1) Amortization of capital equipment	$1,200
2) Service charges	750
3) Film and developing chemicals	750
4) Personnel	4,500
5) Floor space	1,500
6) Utilities and miscellaneous expense	300
Total	$9,000

From the foregoing it is clear that the technical cost per routine chest examination in a large hospital approaches sixty cents. Now let us examine the situation in a small hospital with a capacity of 100 beds. Such a hospital may be expected to have 2,000 or more admissions per year or 8 admissions per day.

In a hospital of this size, it is unnecessary to set up a fully automatic photofluorograph adjacent to the admitting office since the case load is insufficient to warrant such an elaborate installation. Instead it will usually be found that a more economical arrangement can be achieved with little sacrifice in convenience by placing a photofluorographic hood and cut-film camera within one of the rooms of the department of radiology. The capital equipment, including the X-ray generator, rotating anode tube, and tube stand, within a conventional department of radiology today costs approximately $6,000. Also the regular case-load of an X-ray department in a hospital of the size we are considering approaches 16 patients per day. Thus, the additional load of 8 routine chest examinations will increase the total load to 24 individuals. Since the photofluorographic portion of this load constitutes one-third of the total, one-third of the cost of the available capital equipment (or $2,000) should be amortized against the routine chest procedures.

To perform the photofluorographic examinations in such an arrangement, a photofluorographic hood and cut-film camera costing approximately $2,500 will be needed. Thus, if we amortize all of the equipment on a ten-year basis, the annual cost incurred by capital equipment will include $200 for apparatus already at hand and $250 for new equipment. If 2,000 examinations are done each year,

the foregoing figures indicate equipment costs of 10 cents and 12.5 cents per film, respectively.

It may be argued that, in a small hospital performing only 8 routine chest examinations per day, photofluorographic apparatus should not be installed and that the procedures should be performed on regular 14 by 17-inch film. However, 14 by 17-inch film costs approximately 90 cents per exposure. On the other hand, 70 mm. film costs approximately 5 cents per exposure and, as we have just seen, the apparatus in which it is used costs 12.5 cents per exposure.

It is therefore clear that even in a very small hospital, photofluorographic procedures are the more economical. The small films also pose a lesser filing problem than the larger films.

The costs of service, film and developing chemicals, and personnel will be proportionately smaller in the small hospital than those occurring in a large hospital. Where the annual case-load is 2,000, these costs will approach $100, $100, and $600, respectively.

As in the case of capital equipment, the cost assignable to the routine chest examination for floor space is one-third of the total or approximately $500 if the department of radiology uses a total of 500 square feet. The amount used for utilities and extras may be expected to approach $50. Therefore, the technical budget for a small 100-bed hospital performing routine chest examinations might include:

Amortization of capital equipment at hand	$200
Amortization of photofluorographic apparatus	250
Service	100
Films and developing chemicals	100
Personnel	600
Floor space	500
Utilities and extras	50
	$1,800

If 2,000 examinations are performed within this budget, the technical cost per examination will be 90 cents. As will be seen, this amount is only 50 per cent greater than that encountered in a large general hospital. Certainly this difference can hardly be considered significant. Indeed, it clearly indicates that from an economic standpoint mass chest surveys are just as feasible in small hospitals as in the large. Of course, some hospitals may prefer to establish their photofluorographic installations in separate space adjacent to their admitting offices as in the case of large hospitals. This arrangement obviously will be more expensive but even here the cost per examination will usually not exceed $1.50.

Until now, nothing has been said regarding the professional fees of the radiologist who reads the routine chest films of a small hospital. Although it is the custom of large teaching hospitals to make no charge for this service because of the educational value of the films, it seems unreasonable that a physician who makes his living from radiological methods should be expected to forego any

revenue from a procedure that is time consuming from both technical and administrative standpoints. It is therefore firmly believed that a charge, determined by the physician himself, should always be made for the film interpretation unless the physician indicates his willingness to waive this privilege. Although these charges will vary from one community to another, they may be expected to range from twenty-five to fifty cents per film in most places. Therefore, the total cost of the photofluorographic examination in a small hospital when performed under reasonably economical conditions will range from $1.15 to $1.40.

In view of the foregoing it is evident that mass roentgenographic chest surveys in small hospitals are quite practicable. Therefore, since these surveys have proved over and over again to reveal unusually large numbers of asymptomatic persons with tuberculosis, they should be actively promoted by all who are interested in the tuberculosis problem. During 1948, twenty-two small hospitals in Michigan installed photofluorographic equipment with the aid of state and federal funds. With continuing aid from similar sources and with funds made available from the tuberculosis associations of this country, there is no reason why the majority of our small hospitals should not enjoy the established advantages of mass radiographic equipment. Such units could be used not only to serve the hospitals in which they are located but also their surrounding communities. Community surveys could be instituted each year to attract well persons to the small hospitals to yield even greater benefits. Certainly the money spent in small hospitals is money well spent.

RUSSELL H. MORGAN

Notes

THE USE OF A DUBOS-TYPE SOLID MEDIUM CONTAINING PENICILLIN FOR THE PRIMARY ISOLATION OF M. TUBERCULOSIS FROM HUMAN DISCHARGES

The ideal medium for the cultivation of tubercle bacilli from clinical materials has not been defined. Considerable interest has recently been aroused in the use of clear, semi-synthetic media modeled after that described by Dubos and his associates which contained serum and oleic acid[1, 2, 3]. Smith and his associates[4] have added penicillin to the solid form to suppress contaminants and obtained excellent results in the isolation of tubercle bacilli from clinical materials.

The present study was undertaken to evaluate a similar solid medium prepared from TB broth base (Bacto) to which serum, agar, oleic acid, and penicillin were added. It has been compared with an egg-yolk-potato medium recommended by the American Trudeau Society and with the results of guinea pig inoculation.

The clinical materials were submitted to the laboratory for diagnostic study from a general medical service. The procedures were carried out by well-trained, but not highly specialized, technical personnel.

METHODS

Dubos-type medium: The base of the Dubos-type medium was prepared by dissolving 11.6 gm. of TB broth base without Tween 80[5] (Bacto), 2.0 gm. of asparagine (Bacto), and 15.0 gm. of agar (Bacto) in 1,000 cc. of boiling water. The medium was dispensed into 500 cc. flasks in amounts of 200 cc., autoclaved, and allowed to cool. For use, the base was melted, cooled below 50°C., and the following added to each flask aseptically:

1. Dubos medium albumin (Bacto), 20.0 cc.
2. Penicillin solution—10,000 units per cc., 1.0 cc.
3. Oleic acid (0.12 cc. dissolved in 10 cc. of 95 per cent ethyl alcohol), 1.0 cc.

After combination, the medium was poured into small Petri dishes (1.5 by 5 cm.), and allowed to cool. A similar medium lacking oleic acid was studied in parallel in every instance.

Egg-yolk-potato medium:[6] This medium was prepared exactly as described,[7] and was dispensed in two-ounce screw-cap medicine bottles.

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[1] Dubos, R. J., and Davis, B. O.: Factors affecting the growth of tubercle bacilli in liquid media, J. Exper. Med., 1946, *83*, 409.

[2] Dubos, R. J., and Middlebrook, G.: Media for tubercle bacilli, Am. Rev. Tubere., 1947, *56*, 334.

[3] Foley, G. E.: Further observations on the cultivation of tubercle bacilli from pathological material in Dubos medium, J. Lab. & Clin. Med., 1947, *32*, 842.

[4] Smith, J. W., Humiston, J., Creger, W. P., and Kirby, W. M. M.: Evaluation of Dubos' solid medium containing penicillin in the isolation of tubercle bacilli, Proc. Soc. Exper. Biol. & Med., 1949, *70*, 589.

[5] Tween 80 is the proprietary name of the polyoxyethylene derivative of Sorbitan monooleate, obtained from the Atlas Powder Co., Wilmington, Delaware.

[6] Hereafter described as EYP medium.

[7] American Trudeau Society: Report of Committee on Evaluation of Laboratory Procedures: The culturing of specimens suspected of containing tubercle bacilli, Am. Rev. Tubere., 1946, *14*, 428.

Animal inoculation: Guinea pigs were inoculated intraperitoneally, sacrificed, and autopsied after six weeks of observation.

Concentration of materials: Materials believed to be contaminated were treated by rapid agitation in a mechanical shaker in the presence of 4.0 per cent sodium hydroxide solution for ten minutes, followed by immediate neutralization and centrifugation. Uncontaminated specimens were centrifuged without treatment.

Inoculation: The Dubos-type medium was inoculated with several loopfuls of the concentrated sediment. Larger amounts interfered with the discovery of the typical colonies. Approximately 0.3 cc. of sediment was transferred to the EYP medium. A similar amount was diluted, divided into two parts, and injected into guinea pigs when these animals were to be used.

TABLE 1

Comparison of Frequency of Isolation of M. Tuberculosis on Dubos-Type and Egg-Yolk-Potato Media and by Guinea Pig Inoculation

	TOTAL ISOLATIONS	SPUTUM	GASTRIC ASPIRATIONS	URINE	UNTREATED MATERIALS
Guinea pigs inoculated					
Guinea pigs positive	49	9	17	8	17
Both media positive	31	7	10	7	9
EYP, positive; Dubos-type, negative	5	—	3	—	2
EYP, negative; Dubos-type positive	6	1	2	1	3
Both media negative	7	1	2	—	3
Guinea pigs negative	3	—	1	1	1
Both media positive	1	—	1	—	—
EYP, positive; Dubos-type, negative	2	—	—	1	1
Guinea pigs not inoculated					
Both media positive	53	32	5	8	12
EYP, positive; Dubos-type, negative	14	5	2	2	7
EYP, negative; Dubos-type, positive	39	25	6	5	6
Total positive cultures	106	62	13	15	25
Total	158	71	30	24	43

Incubation: The plates containing Dubos-type medium were sealed after inoculation with Scotch tape and placed in an incubator with a high humidity. The latter feature prevented peeling of the tape and drying of the medium. The bottles of EYP medium were incubated in parallel. All cultures were examined at weekly intervals. The typical colonies of tubercle bacilli were sought on the Dubos-type medium by direct examination through the bottom of the Petri dish under low power of an ordinary microscope. All suspicious colonies on either medium were demonstrated to be acid-fast bacilli by appropriate staining methods.

Stained smears were prepared of scrapings from the surface of the EYP medium after thirty days of incubation even though no colonies were to be seen.

RESULTS

Tubercle bacilli were recovered from 158 specimens. The data are presented in table 1.

Guinea pigs were inoculated with 52 of the specimens and were positive on 49 occasions. Tubercle bacilli were isolated on both media in 31 of the 49 specimens positive on

animal inoculation. In 7 of the specimens positive for tubercle bacilli on animal inoculation, no growth of *M. tuberculosis* was obtained on either medium. One or the other medium was negative for *M. tuberculosis* when planted with the remaining 11 specimens positive on animal inoculation. When both media were employed, the cultural procedure failed to recover tubercle bacilli in 14 per cent of the examinations. If only one medium had been employed, the elimination of animal inoculation would have resulted in a 26 per cent less frequent recovery of tubercle bacilli. It should be noted, however, that isolation of the organism by culture was accomplished three times when the animal inoculation was negative.

Neither the type of material studied nor the method of concentration significantly affected the results.

Tubercle bacilli were isolated by cultural methods from 106 specimens in which animal inoculation was not done. Both media were positive in 53. In 14 of the remainder, the EYP medium was positive and the Dubos type was negative; in 39, the reverse was true.

TABLE 2

Time Required for Growth of M. Tuberculosis on Dubos-Type and Egg-Yolk-Potato Media

MEDIUM	TOTAL ISOLATIONS	WEEK IN WHICH GROWTH OF TUBERCLE BACILLI WAS FIRST DETECTED													
		1		2		3		4		5		6		7	
		Number	Cumulative per cent	Number	Cumulative per cent	Number	Cumulative per cent	Number	Cumulative per cent	Number	Cumulative per cent	Number	Cumulative per cent	Number	Cumulative per cent
Dubos	129	1	0.8	33	26.4	43	59.8	30	83.0	14	93.8	7	99.2	1	100.0
EYP	104	0	0.0	1	0.9	22	22.1	33	53.9	26	78.9	12	90.4	10	100.0

If this group of results be combined with the first described above, it will be observed that both media were positive in only 56 per cent of these isolations of tubercle bacilli. The EYP medium alone was successful in approximately 14 per cent, and the Dubos-type alone in approximately 30 per cent. This favorable result was attained in spite of the fact that the inoculum on the latter medium was very much smaller than on the former. The data suggest that the Dubos-type medium was more successful than the EYP medium in the recovery of these organisms from sputum.

The Dubos-type medium, with and without oleic acid, was compared on every examination but the results need not be described in detail. Three strains of tubercle bacilli (1.9 per cent) isolated on Dubos-type medium without oleic acid failed to grow on repeated attempts at subculture in the presence of penicillin and oleic acid. They were not tested on the medium without antibiotic but containing oleic acid. All of the others grew much more luxuriantly on the medium in which this substance had been incorporated. Typical cord formation occurred regularly on this medium, and the detection of colonies of tubercle bacilli under the microscope was very simple.

Contamination was a rare event with either medium. Only 2 of the Dubos and 5 of the EYP preparations were discarded because of overgrowth with other organisms.

The results of an analysis of the earliest appearance of detectable growth on the two media are summarized in table 2. Only those specimens are included in which complete temporal data were available.

Tubercle bacilli were isolated much more promptly on the Dubos than on the EYP

medium. One-quarter of the cultures on the former were found to be positive during the second week and 80 per cent were positive by the end of the fourth week. Similar results on EYP medium required one additional week of incubation.

COMMENT

A Dubos-type, clear, solid medium containing oleic acid and penicillin and contained in small Petri dishes has proved to be quite satisfactory for the primary isolation of tubercle bacilli from clinical materials. All of the components are available commercially in package form, permitting rapid and simple preparation. It is essential that the base without Tween 80 be used. This medium has proved to be substantially superior to the egg-yolk-potato medium recommended by the American Trudeau Society. This result was attained in spite of the use, for technical reasons, of a much smaller inoculum in the Dubos-type medium.

Neither medium alone compared favorably with guinea pig inoculation as a method for the recovery of this organism. When both were employed simultaneously the results were better, although animal inoculation was still superior. Isolation of tubercle bacilli was accomplished about one week earlier, on the average, with the Dubos-type medium.

These results demonstrate that neither the Dubos-type nor the egg-yolk-potato medium can be regarded as satisfactory for the definitive recovery of tubercle bacilli from clinical materials when used alone. A technique employing both gives a very high rate of isolation of these organisms and is not technically too complex for the ordinary laboratory. Its use is to be strongly recommended to the laboratories of general hospitals and clinics where the primary diagnosis of tuberculosis of a variety of sites must be constantly attempted.

SUMMARY

A Dubos-type, clear, solid medium containing oleic acid and penicillin has been demonstrated to be substantially superior to an egg-yolk-potato medium for the primary isolation of tubercle bacilli from clinical materials.

Neither medium used alone compared satisfactorily with guinea pig inoculation for the same purpose.

The use of the two media in parallel gave a high rate of recovery of tubercle bacilli and should be a valuable technique for the diagnosis of tuberculosis.

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THE USE OF TUBERCULIN-TREATED ERYTHROCYTES AS AN ANTIGEN IN ELICITING CUTANEOUS HYPERSENSITIVITY TO TUBERCULIN

In view of the continued interest in the Middlebrook-Dubos hemagglutination test and certain modifications thereof, the following observations may be of general interest. Middlebrook, Dubos, and Boyden have indicated that at least two and possibly three tuberculin antigens, one of them probably a protein, are involved in the test. The present writers have found that one of the antigens adsorbed to the red cell is capable of eliciting a typical tuberculin response in tuberculous rabbits and is therefore presumably a protein.

During the course of investigations into the nature of the antigen(s) adsorbed in the test, the writers used a suspension of tuberculin-treated erythrocytes as an intradermal skin-test antigen. Sheep erythrocytes were treated in the manner prescribed by Scott and Smith (J. Lab. & Clin. Med., 1950, *35*, 303) and made up in 40 per cent suspension in buffered saline. Controls of untreated cells and dilute tuberculin (1:10) were used. Injection of 0.1 ml. of these cell suspensions into tuberculous and normal rabbits showed an early, nonspecific erythema which gradually disappeared. In the tuberculous animals, the erythema was replaced in 48 to 72 hours by an edema and induration at the site of inoculation of the treated cells. That the antigen could be partially eluted by heating to 45°C. for 30 minutes was shown by the fact that the eluate elicited a tuberculin-type reaction upon intradermal injection into tuberculous animals.

The above has been repeated in 4 tuberculous and 7 normal rabbits with comparable results. Cells from the test animals were used as antigen carriers. Both treated and normal cells and treated and normal erythrocyte stroma were used. Two rabbits previously inoculated (6 months) with BCG failed to give the reaction. They also failed, however, to react to tuberculin or PPD. Two rabbits were tested at an early stage of tuberculosis (*M. tuberculosis*, Ravenel, subcutaneous, 3 weeks previous to test). One failed to react, while the other gave a slightly positive test. In all cases the reaction to tuberculin-treated erythrocytes paralleled that to dilute tuberculin. The reaction to treated stroma gave a more pronounced early, nonspecific edema than did treated cells and also a more pronounced late, specific edema and induration. The latter often progressed to necrosis in four to five days.

It is believed that the adsorption of this antigen may be important in over-all evaluation of the Middlebrook test.

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American Trudeau Society

Medical Section of the National Tuberculosis Association

THE AWARD OF THE TRUDEAU MEDAL FOR 1951

The Trudeau Medal for 1951 was awarded to Dr. René J. Dubos of the Rockefeller Institute for Medical Research on May 16, 1951 at the annual meeting of the National Tuberculosis Association. The presentation was made by Dr. Esmond R. Long on behalf of Dr. Florence Sabin who was unable to be present. Doctor Sabin's remarks and the response of Doctor Dubos follow:

Doctor Sabin (read by Doctor Long): Two lines of thought can be traced throughout the studies of our candidate and his staff, the pursuit of the chemical nature of the virulence of the tubercle bacillus and the study of factors in the host which affect the bacillus and contribute to resistance of the body to infection.

In the study of tuberculosis, the development of different media for growing the bacilli has played a greater role than with any other organism. The slow growth of tubercle bacilli and their limitation to the surface of liquid media made the original techniques difficult of mastery. Extensive modifications of methods have been made to study growth requirements; to adapt the media for growing the bacilli from sputum and tissues for diagnosis; to obtain massive growth for chemical analyses; to use synthetic media without protein, such as Long's, for procuring tuberculo-protein, as developed by Seibert; and to adapt the media for dissociation and for the needs of experimental work.

The classic method of growth of the organism on the surface of liquid media in pellicles or large clumps gives extreme heterogeneity to the culture, organisms living and dead, the living young and active as well as in all stages of asphyxiation and starvation, the dead in all stages of disintegration.

Our candidate, using the newer chemical knowledge of detergents, has shown that the dry character of the organisms on the surface of liquid media is due to the bacilli being markedly hydrophobic. This is not surprising since the lipid most characteristic of the bacilli—as it gives acid-fastness, the mycolic acid of Anderson's analyses—cannot possibly be wet with water. By studying many detergents now in use in industry, one, its trade name being "Tween 80", has been found favorable for growing tubercle bacilli dispersed in the media. "Tween 80" is a complex molecule, a polyoxyethylene derivative of sorbitan oleate. Our candidate has illustrated in a diagram the possible action of the compound, showing the esterified fatty acid as attached to the lipoidal surface of the bacillus while the rest of the molecule with its hydroxyl groups presents a hydrophilic surface to the media. To this great stride forward has been added another, the use of a little serum albumin which combines with traces of free fatty acids in the media which powerfully inhibit the growth of tubercle bacilli. The serum albumin thus removes inhibitors while the Tween converts the hydrophobic bacillary surface to a hydrophilic one and for the first time rapid, diffuse growth becomes possible. Here then is a new method for obtaining homogeneous cultures of young, living, relatively fast-growing organisms, comparable to cultures of those organisms which have formed the foundations of our knowledge of immunology.

No one technique for growing acid-fast organisms answers all purposes and, if one were to select the most significant characteristic effect of the classical technique, it would be

perhaps that by chance it gave us tuberculin and so laid the foundation of allergy and allowed the study of the role of allergy in tuberculosis. But, by its very heterogeneity, it was ill adapted to unravel the nature of virulence. On the other hand, the supreme advantage of the new technique for dispersed, submerged growth is to open up the long road to the study of the chemical nature of virulence in tubercle bacilli and lay the foundation for the study of their immunology as it has been worked out for the pneumococcus.

Concerning virulence, it has been observed that virulent tubercle bacilli grow in cords with the bacilli all parallel and forming serpentine patterns. Our candidate shows these serpentine cords illustrated in Koch's original publications; moreover, the pattern has been seen again and again, for example, in moving pictures of growing tubercle bacilli which Doctor Wyckoff presented some years ago to this society. Our candidate has gone farther; all virulent tubercle bacilli grow in serpentine cord formation; all completely avirulent organisms grow haphazardly; but some intermediate strains without power to produce disease may grow in serpentine cords. Reasoning that, since the addition of a wetting factor prevents virulent organisms from growing in cords, there may be a special hydrophobic lipid on the very surface of the bacilli, such as has been extracted by Bloch with petrolic ether, our candidate has found that repeated small injections of this crude lipid give pulmonary lesions causing death in mice.

Virulent tubercle bacilli washed and placed in a buffered solution containing neutral red, take up the dye from the yellow solution and turn it into the brilliant red salt. Avirulent bacilli entirely lack this power. This might be a clue to the true virulence factor, and it is certainly the first chemical distinction unique for virulent strains.

Turning to host factors, it was found that with these young cultures mice could be used exactly as well as guinea pigs with great saving of money and time. Taking caseation as the characteristic of the disease most distinctive from other infections, the observation which has been long a mystery, namely, that very few bacilli can ever be stained in the center of closed caseous areas while when they open into a bronchus or into a blood vessel enormous multiplication takes place, has led to the following studies. Our candidate has found by testing with this new technique that many fatty acids, such as may well be present in caseous material, inhibit the multiplication of tubercle bacilli but do not kill them. This may well be one factor as well as lowered oxygen tension.

The last work reported is that a substance has been extracted from the kidney of guinea pigs, and from organs of other animals as well, with which complete inhibition of growth can be obtained even with large inocula. It works better with attenuated than with fully virulent strains.

The advantages of these new methods are young homogeneous cultures, more rapid growth, chance to know the number of organisms used experimentally, growth from small inocula, down to 2 or 3 bacilli, an accurate technique for qualitative and quantitative tests of the effects of different substances on the bacilli, the accurate determination as to whether the effect is bacteriostatic or bactericidal, a chance to obtain more stable cultures of BCG and, most significant of all, the opening up of the study of the chemical nature of virulence.

The practical consequences of this fundamental work for future research would be hard to overestimate, but immediate advantages have not been overlooked as, for example, in studies of a new diagnostic test with sensitized sheep erythrocytes not yet wholly evaluated but of real promise.

Doctor Dubos has shown the same keen, critical judgment in presenting his own experiments as he evinced in his recently published *Life of Pasteur*. Here is set down the full meaning of scientific research, a grasp of the nature of the methods and the

motives in research, together with a living picture of the man, so vivid that it puts this book among the great biographies of history.

From following the work of Dr. René Dubos in tuberculosis, marking a new period in the study of this disease, your committee grants him the Trudeau Medal in the conviction that if Trudeau, himself, were among us tonight, he would take great pleasure in this work.

Doctor Dubos: I have several reasons to be deeply moved by the honor that you have conferred upon me. First, of course, is the sense of personal gratification that you have deemed worthy of the Trudeau Award that phase of my scientific studies nearest to my heart, namely, the problem of the pathogenesis of tuberculosis. I take much pleasure also in recognizing among the membership of the award committee the name of several friends, in particular that of Dr. Florence Sabin whose place I occupy at the Rockefeller Institute. In addition there come to my mind other thoughts that transcend these personal considerations. They concern both the scientific institute of which I am the representative tonight and your own organization.

As many of you know, the Rockefeller Institute for Medical Research was organized some fifty years ago to provide a place where certain individuals could devote themselves to scientific investigations, protected from the pressure of practical problems and free of routine duties. Little is asked of us except that we try to exercise judgment in selecting problems of broad interest, and devote to them all of our efforts and abilities. At the most, it is hoped that the results of our work will some day contribute in some manner to the welfare of mankind.

By its very nature, the National Tuberculosis Association must take a very different attitude. It is dedicated to the practical solution of a very specific problem, the control of tuberculosis. Your duty is to convert into practical operations all knowledge available on the subject. Mortality and morbidity statistics are before you every day to emphasize the urgency of your mission. But the founders of your organization, as well as its present administrators, have realized that existing knowledge may not be sufficient to allow the complete eradication of tuberculosis. For this reason, they have made it a cardinal part of their policy to encourage many lines of free and theoretical research which may in the future have some bearing on the problem of disease.

Whereas the germ theory of disease gave a rational basis to the empirical sanitary measures initiated in the 1830's and thus led to a more effective fight against the spread of bacilli, no similar body of scientific doctrine has come to guide the antituberculosis movement in its efforts to render man more resistant to infection. There is as yet no clear understanding of the mechanisms by which the body can ward off infection or progressive disease, and there is no way of measuring either inborn resistance or acquired immunity. This ignorance greatly handicaps all efforts to develop methods for producing a truly effective specific immunity. At first sight, the situation appears more satisfactory with reference to the medical techniques used in the management of the tuberculous patient since the practices codified in sanatorium life, whether carried out in a city hospital or in a secluded country resort, are unquestionably of benefit both to the patient and to society. But it is not unlikely that the same results could be obtained with more certainty, less time, and at lower cost of human and economic values if precise knowledge were available of the factors that affect the course of tuberculosis.

The important advances are likely to come from the workers who stray from the obvious paths and venture into unexplored areas. But it is not easy to integrate these temperamental trail blazers into the rigid and cumbersome structure of large educational or

research institutions and of governmental bodies. For this reason voluntary and unofficial agencies have an important role to play in searching, recognizing, and encouraging unorthodox approaches to the study of tuberculosis. It took much boldness of spirit to establish in the 1900's the new philosophy that permitted physicians and the public to work together. It will take much imagination and vision to foster the development of new research concepts, of new points of view, within the ever-growing rigidity of our social framework.

Those of us who function in the ivory towers of science at times find its atmosphere somewhat chilly, and are disheartened by the apparent futility of abstract scientific work. We often envy you who apply the products of science to such obviously useful ends. However, the award of the Trudeau Medal tonight gives us the confidence that you value our efforts. It is a symbol of the fact that, in final analysis, our goal is the same as yours. Allow me to thank you for the award in the name of my fellow workers in the experimental sciences.

NOTES

ANNUAL MEETING—1952

The annual meeting of the American Trudeau Society will be held in connection with the annual meeting of the National Tuberculosis Association in Boston, Massachusetts, from May 26 to May 29, 1952. Members of the Society wishing to submit titles for consideration by the Program Committee should communicate with Dr. Theodore L. Badger, Chairman of the Medical Sessions Subcommittee of the Annual Meeting Program Committee not later than October 1, 1951.

DR. JAMES E. PERKINS' TRIP TO WEST GERMANY AND PARIS

Dr. James E. Perkins, managing director of the National Tuberculosis Association, is planning to spend six weeks in Western Germany this summer as a member of a seven-man team of public health experts who will conduct a series of public health planning institutes under the auspices of the Unitarian Service Committee with the cooperation of the Health and Welfare Division of the Office of the U. S. High Commissioner for Germany. The project is made possible through a grant from the Oberlaender Trust of Philadelphia. Doctor Perkins went to Germany on June 26. He will remain in Europe after the institutes end, about August 20, for the Conference of Executive Directors of National Tuberculosis Associations and meetings of the Executive Committee and Council of the International Union against Tuberculosis in Paris in early September.

IX CONGRESO PANAMERICANO DE LA TUBERCULOSIS
UNIÓN LATINO-AMERICANA DE SOCIEDADES DE TISIOLOGÍA

The IX Congreso Panamericano de la Tuberculosis (U.L.A.S.T.) met in Guayaquil and Quito, Ecuador, from July 14 to July 22, 1951 under the presidency of Dr. Jorge A. Higgins. It was attended by 135 delegates. At the invitation of the Organizing Committee, the following members of the National Tuberculosis Association and the American Trudeau Society participated in the meeting as observers: Dr. Floyd M. Feldmann, Mr. and Mrs. F. D. Hopkins, Dr. Herbert L. Mantz, Dr. Gilberto S. Pesquera, and Dr. Esmond R. Long.

Prior to the meeting in Ecuador, these representatives spent three days in Panama and the Canal Zone at the invitation of the Department of Health of the Canal Zone and the local tuberculosis association. After the meeting, all of the representatives visited the Ministry of Public Health and Social Service in Lima, Peru, at the invitation of Dr. L. Cano Gironda, medical chief of the Department of Tuberculosis.

THE AMERICAN REVIEW OF TUBERCULOSIS

ABSTRACTS

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CLINICAL STUDIES, TUBERCULOSIS

Extrapleural Pneumothorax.—In the past ten years, extrapleural pneumothorax has been performed for 600 cases of pulmonary tuberculosis. The advantages are: (*1*) It produces no deformity; (*2*) it is performed in one stage; (*3*) it gives a more selective collapse than any other procedure, even thoracoplasty. Its reversibility is an advantage in some cases and a drawback in others. It can, however, be made permanent after one year, at which time refills are required only once a month. The disadvantages are: (*1*) It may be impossible to establish. This happened in 3 per cent of the cases. A thoracoplasty then can be done. (*2*) It is easy to lose the space. Up to three months, the pressure must be observed closely. After this, there is very little risk. (*3*) Tearing the pleura with creation of an intrapleural pneumothorax (4 per cent). Combining the spaces does not work out well. It is best to reinflate the lung, close the wound, and try again in a few months. (*4*) Bleeding which could not be controlled by ordinary means (one per cent). (*5*) Postoperative oozing ranged from 1 to 2 liters. This may be serious. (*6*) Nontuberculous infection occurred in 29 cases (5 per cent) with 7 deaths. Many of these took place in the pre-penicillin era. None of the above complications are particularly dangerous. (*7*) More serious is tuberculous empyema and bronchopleural fistula. There were 73 cases of empyema (12 per cent) with 12 deaths and 28 cases of bronchopleural fistula (4.7 per cent). The latter usually arose from large superficial cavities. Favorable patients were those with cavities less than 4 cm. in diameter and not located below the fifth rib, and with a vital capacity of at least 2,500 cc. In this group of 107 cases, there were 2 deaths, 2 with pulmonary complications, and 2 empyemas. Negative sputum was achieved by 101 patients and 89 (88 per cent) remained negative for one to eight years. In cases with less favorable criteria, the results were correspondingly poorer.—*Extrapleural pneumothorax in the treatment of pulmonary tuberculosis, E. Murstad, Lancet, February 10, 1951, 1: 299.*—(*A. G. Cohen*)

Cavernostomy for Residual Cavity.—Since 10 to 20 per cent of thoracoplasties fail because of residual cavities, the insertion of a Monaldi catheter concomitantly with the thoracoplasty was tried without altering the final results. At present, resection is given first consideration but some patients are not suitable risks. Open cavernostomy in 2 stages was used to obliterate such cavities, utilizing streptomycin to permit early closure of the resultant sinuses. After 3 successive cultures of both sputum and drainage material are negative and planigrams indicate closure of the cavity, the tract is excised, a pedicle graft of muscle is buried in the defect, and the skin is closed. In a series of 23 patients so treated, traumatic pneumothorax occurred during 4 operations, with one death; 16 patients have had the sinus closed; 7 still have a draining sinus but 3 of these are recent cases. The remaining 3 patients were poorly selected and did not meet the prerequisite of Le Carboulec that the cavity must represent the sole remaining focus of disease.—*Cavernostomy for residual cavity after thoracoplasty, J. D. Murphy & E. R. Koontz, J. Thoracic Surg., August, 1950, 20: 222.*—(*R. E. MacQuigg*)

Tuberculous Empyema.—The authors believe that repeated aspiration deserves a

thorough trial in tuberculous empyema. Accordingly, 61 patients were treated in this manner, aspirations being performed every two to three days. Treatment lasted from two months to three and a half years, with an average of thirteen and a half months. Complete obliteration of the pleural space took place in 45 (75 per cent). Of these, there was reactivation of the tuberculosis in 8; 4 had a poor collapse to begin with and 33 are well. In 8 cases, aspiration treatment was interrupted in favor of thoracoplasty in order to control the pulmonary lesion. The chances of reactivation are much greater in patients with anatomically poor, even though effective, collapse than in patients with anatomically good and effective collapse. In 8 cases, the lung failed to re-expand.—*The treatment of tuberculous empyema by aspiration, A. H. M. Siddons & M. L. Konstam, Tubercle, April, 1951, 32: 85.*—(*A. G. Cohen*)

Pulmonary Resection for Tuberculosis.—Partial or complete lung resection for pulmonary tuberculosis was performed between 1944 and 1949 in 60 cases. Half of the patients were between the ages of twenty and twenty-nine. Indications for resection were failure of thoracoplasty due to bronchiectasis or persisting cavitation in 22 patients; tuberculous bronchiectasis in 10; bronchostenosis in 9, 8 of whom were women; basal cavities in 9; tuberculomas in 4; a totally destroyed lung in 2; and an apical cavity with an adherent lung in one child of seven. In 3 cases the operation was elective. Postoperatively, 40 patients improved, 4 became worse, and in one patient the disease appeared stationary. There were 15 deaths, 8 within two months of operation, an over-all operative mortality of 13.3 per cent. Best results were obtained in those patients operated upon for tuberculomas, bronchiectasis, and bronchostenosis. Streptomycin was employed in 50 cases. Spread of the disease with or without bronchopleural fistula was the most important serious complication occurring in 9 of the 20 total resections and in 7 of the 40 subtotal resections. Spread developed following bronchopleural fistula in 9 patients and followed reactivation from overdistention in 7. The complications of bronchopleural fistula, empyema, and spread developed in 10 per cent of the patients treated with streptomycin and in 40 per cent of those who did not receive the drug. The greatest number of complications followed total pneumonectomy and the fewest followed segmental resection. The results of subtotal resection were better than those following total resection. Among 42 patients with a positive sputum preoperatively, only 20 became negative following operation. In 5 of the patients with a positive sputum persisting postoperatively, no source for the positive sputum could be demonstrated. The incidence of the most common complication, bronchopleural fistula, was markedly reduced when constant suction was used for rapid re-expansion of the lung following segmental resection and lobectomy. —*Experiences with lung resection in pulmonary tuberculosis, V. D. Schaffner, J. J. Quinlan, & J. E. Hiltz, Canad. M. A. J., April, 1951, 64: 326.*—(*E. A. Riley*)

Resection for Tuberculosis.—When a tuberculous lesion has progressed to such an extent that the chances of ultimate healing are uncertain under any other form of treatment and it yet remains localized to a removable part of the lung, the ideal treatment is resection. The authors treated by resection patients whom in the past they would have submitted to thoracoplasty. At an early stage in the treatment, a general plan was laid down and temporary collapse measures sometimes were required. Streptomycin, 1.0 gm. daily, was given for one week before, and six weeks after, the operation. After pneumonectomy, the amount of dead space was reduced by phrenicotomy supplemented by pneumoperitoneum for six weeks. Following lobectomy, some of the authors crushed the phrenic nerve; others did not. After an upper lobectomy, an apical thoracoplasty sometimes was used if it was not possible to induce pneumoperitoneum or if the opposite apex was suspected of being diseased and any medi-

astinal deviation was considered undesirable. A total of 250 resections have been done. There were 5 deaths within three months of operation, giving a mortality rate of 2.5 per cent. Empyema and bronchopleural fistulas were the most serious complications. A follow-up of 100 patients who had been operated upon six months or more previously showed arrest of the disease in 90.8 per cent of the cases.—*Lung resection for pulmonary tuberculosis, B. J. Bickford, F. R. Edwards, J. R. Esplen, J. H. Gifford, A. M. Mair, & O. F. Thomas, Thorax, March, 1951, 6: 25.*—(*A. G. Cohen*)

Pulmonary Resection for Tuberculosis.—Among 111 pneumonectomies, 73 lobectomies, and 16 segmental resections performed since May 1943 for tuberculosis, the postoperative mortality has been 4.5 per cent. All deaths occurred after pneumonectomy, chiefly in patients who were bad risks. Subsequently the death rate has been reduced to 3.8 per cent; after 258 resections there have been 10 deaths. Besides these deaths 4 patients have died more than six months postoperatively. On October 1, 1950, 187 patients survived; in 172 (92 per cent) the sputum had become negative. In 170 instances the condition of the patient was good and in 13, fair; in the remaining 4 cases the prognosis was considered bad. Of the 117 patients who had returned home, 104 were again at work; 70 patients were still under treatment in the sanatorium. In the first 143 patients observed more than six months, the result was good, 123 (90 per cent) having negative sputum.—*Lobectomie, Segmentale Resectie en Pneumonectomie Wegens Longtuberculose op Grond van een Persoonlijke Operatiestatistiek van 200 Gevallen, L. D. Eerland, Nederl. tijdschr. v. geneesk., January 27, 1951, 95: 275.*—(*J. van der Vate*)

Transscapular Thoracoplasty.—Wound infection in thoracoplasty is more uncommon than is generally believed and is invited by leaving "dead space." Infection of the extrapleural space can be avoided by resecting the lower half of the scapula during the first stage. The author reports 72 cases without infection in which he resected a segment of the fourth rib, followed by complete resection of the third, second, and first ribs in that order. Division of the infraspinatus muscle and a few fibers of the trapezius yielded adequate exposure; postoperative recovery was quick because of the minimal trauma.—*Transscapular thoracoplasty, A. Coello, J. Thoracic Surg., June, 1950, 19: 900.*—(*R. E. MacQuigg*)

Late Results of Thoracoplasty.—Uniform methods of modern thoracoplasty were used for 424 patients in a Copenhagen hospital during the years 1935 to 1941. Only 4 patients were above 50 years of age; none was below 15 years. Generally pneumothorax was first tried but cavities were definitely present before operation in 87 per cent. The follow-up during at least two years was 100 per cent in spite of the war. Of the surviving patients 67 per cent were healthy, roentgenologically stationary, abacillary on culture, and without serious complications. The permanent results were far superior to those obtained by conservative treatment particularly among "good chronics," only 20 to 25 per cent of whom remain well without operation. In the few cases of bilateral cavity neither conservative treatment nor thoracoplasty showed good results. Good results appeared within the first two years following operation, after which time the condition remained fairly constant.—*Late results in four hundred twenty tuberculous patients subjected to thoracoplasty, F. Hagn-Meincke, J. Thoracic Surg., June, 1950, 19: 837.*—(*R. E. MacQuigg*)

Tuberculosis of the Nasolacrimal Duct.—The nasolacrimal duct very rarely becomes tuberculous. A case occurred in a boy aged fourteen months, who also had involvement of the cervical nodes. Examination of the nose and eyes was negative. The condition temporarily improved after streptomycin, then relapsed and surgery was required. It is believed that this was a primary infection,

the source being a tuberculous father.—*Tuberculosis of the nasolacrimal duct, P. G. Konstam & M. J. Meynell, Lancet, February 24, 1951, 1: 444.*—(*A. G. Cohen*)

Tuberculosis of the Hip.—The authors' preferred treatment of tuberculosis of the hip in children is surgical arthrodesis. This is performed as early as possible in the course of the disease. Antibiotics seem to have no influence on the course. A prerequisite for operation is the roentgenographic demonstration of signs of localization. A warm abscess is a contraindication to surgery but a cold abscess is not. The optimal stage usually is reached after one and a half to two years of conservative management. Early weight bearing in a walking spica is encouraged. Even very young children can be operated upon successfully.—*Early surgical therapy of tuberculosis of the hip in children, W. M. Roberts & F. S. Webster, Surg., Gynec. & Obst., February, 1951, 92: 155.*—(*A. G. Cohen*)

CLINICAL STUDIES, NONTUBERCULOUS DISEASES

Pneumonia with Retinal Cytoid Bodies.—A peculiar fatal pneumonia associated with retinal cytoid bodies was observed in 3 patients, a 35-year-old Negro man, a 55-year-old Negro woman, and a 65-year-old white woman. The disease began insidiously and all died within three to six months with progressive pulmonary insufficiency, fever, weight loss, malaise, and cough. Cytoid bodies in the fundi and moist basalar rales were the only significant physical signs. The white blood count remained normal. Roentgenograms demonstrated progressive extension of a diffuse infiltrative process throughout the greater portion of the lung fields. The pathologic findings are considered unique and were characterized by: (*1*) the presence of a thick, eosinophilic, hyaline membrane lining the walls of many alveoli; (*2*) edema and frequently hemorrhages filling many alveoli, inflammatory cells being sparse; (*3*) extensive organization of the alveolar exudate by recently formed connective tissue; and (*4*) the extension of metaplastic bronchiolar epithelium into neighboring areas. In each case typical cytoid bodies were found in the nerve fiber layer of the retina. There was widespread organization of the lung, in addition to alterations in the alveoli and bronchial tree, previously ascribed to pneumonitis of viral or anaphylactic origin or to intoxication with beryllium or the war gases. The cause is obscure, none of the patients having been exposed to toxic materials, and no bacteriologic agent having been isolated. Changes generally associated with collagen-vascular disease were not present. Clinical and pathologic features suggest that this illness is a peculiar form of viral pneumonitis with widespread fibrous organization of the lungs but it may be an unusual, localized form of collagen-vascular disease progressing to pulmonary fibrosis.—*A peculiar pneumonia associated with retinal cytoid bodies, P. A. Tumulty, M. Berthrong, & A. McG. Harvey, Bull., Johns Hopkins Hosp., March, 1951, 88: 239.*—(*J. S. Woolley*)

Pattern of Pneumonia.—The picture of pneumonia is changing as a result of chemotherapy. The cases seen in hospitals are chiefly those which fail to respond to treatment. When investigated, these cases do not show any specific bacterial offender and are designated as primary atypical pneumonia. The manifestations are pleiomorphic and the course is unpredictable. The fever is moderate; the amount of expectoration is slight and rarely bloody; early pleuritic involvement is rare. The fever usually precedes the appearance of abnormal physical signs by a few days. There is occasional transitional jaundice. Cold agglutinins are present. The diagnosis thus rests on the presence of fever, absence of leukocytosis, failure to respond to penicillin and sulpha drugs, presence of cold agglutinins, and positive roentgenographic signs. All of these features need not be present. There are 4 clinical types, all characterized by some proportion of atelectasis: (*1*) Segmental; this is very similar to tuberculosis; (*2*) Lobar collapse and consolidation; this is common and

is very slow in resolving; (3) Bronchopneumonic; this is uncommon and is associated with severe prostration; (4) Migrating and relapsing type; pleural effusion containing leukocytes is common but empyema is rare.—*The changing pattern of pneumonia, A. L. Wingfield, Brit. J. Tuberc., January, 1951, 45: 127.*—(*A. G. Cohen*)

Kartagener's Syndrome.—The triad of bronchiectasis, sinusitis, and situs inversus was first described in 1933. The occurrence of situs inversus has been variously estimated as one in 24,000 cases to one in 6,120 cases. Kartagener and Horlacher showed a 20 per cent incidence of bronchiectasis among patients who had congenital dextrocardia. Olsen reviewing the files of the Mayo Clinic found that 16.5 per cent of patients with true dextrocardia showed definite evidence of bronchiectasis, whereas in the same twenty-two-year period of observation, a diagnosis of bronchiectasis was made in less than 0.5 per cent of the total number of patients who registered at the Mayo Clinic. It is thus apparent that the relationship between dextrocardia, bronchiectasis, and other congenital defects is hardly coincidental. Two cases occurred in a brother and sister, both of whom coughed persistently from early infancy; in one there was also an anomalous left subclavian artery. The authors believe that the bronchiectasis in these patients was of congenital origin.—*Kartagener's syndrome with an anomalous left subclavian artery, J. Kay & R. N. Meyer, Brit. J. Radiol., January, 1951, 24: 27.*—(*B. Hyde*)

Hilar Nodes in Erythema Nodosum.—Hilar adenopathy is associated with the usual signs of erythema nodosum in some cases but has not been recognised generally as an accompaniment of the condition. In a series of 100 consecutive patients with erythema nodosum, roentgenography revealed hilar adenopathy in 9, in 8 of whom the adenopathy was bilateral. Follow-up films of 5 patients were available; in 3 the hilar enlargement had disappeared within one to seven months, and in a fourth the thoracic film was negative twenty months after the initial examination. The one patient whose hilar changes persisted for seven months after the initial examination also had persisting cutaneous lesions of erythema nodosum. With respect to preceding and associated diseases, 4 of the 9 patients had symptoms of an infection of the upper part of the respiratory tract prior to the appearance of erythema nodosum, one had diabetes, one had an alveolar antral fistula, and 3 had no other disease prior to the onset of the erythema nodosum although one of the 3 had sustained an emotional shock.—*Erythema nodosum: The possible significance of associated pulmonary hilar adenopathy, C. C. Johnson, N. O. Hanson, & C. A. Good, Ann. Int. Med., April, 1951, 34: 983.*—(*T. H. Noehren*)

Meigs's Syndrome.—Fibroids of the uterus and ovarian tumors of many types, both benign and malignant, may be accompanied by ascites, hydrothorax, or both. The cause is unknown and it is difficult to understand why some patients with little or no ascites have massive hydrothorax. In one patient with an ovarian teratoma largely composed of thyroid tissue, hydrothorax was suspected but was not prominent. Another patient had papillary adenocarcinoma of the ovaries and retroperitoneal lymph nodes, ascites, and hydrothorax. The peritoneum was normal at operation and there was no roentgenographic evidence of pleural or pulmonary metastases. The fluid in this latter patient did not reaccumulate for twenty-nine months after removal of the tumors, despite transperitoneal biopsy of the retroperitoneal mass. It is suggested that the term "Meigs's syndrome" include all cases of pelvic tumor in which no explanation can be found for these accumulations of fluid in abdomen, chest, or both. By definition, this fluid should be "cured" by removal of the tumor. Exploratory laparotomy is recommended in all patients showing a pelvic mass and ascites, hydrothorax, or both.—*Pelvic tumors with ascites, hydrothorax, or both (Meigs's syndrome),*

K. Nelson & C. W. Dennison, Ann. Int. Med., April, 1951, 34: 1055.—(T. H. Noehren)

Auricular Fibrillation and Mediastinal Tumor.—A 63-year-old woman was seen with frequent attacks of paroxysmal auricular fibrillation. A chest roentgenogram showed a nodular mass in the left mediastinum in the region of the pulmonary outlet. Paroxysmal auricular fibrillation occurred when the patient was lying on her left side or when she assumed the erect posture; it did not occur when she was lying on her right side. On the basis of a cervical lymph node biopsy the diagnosis of lymphoma of low-grade malignancy was made. Following X-ray therapy there was reduction in the size of the mediastinal mass and the attacks of paroxysmal auricular fibrillation disappeared.—*An unusual case of paroxysmal auricular fibrillation due to mediastinal malignant lymphoma, W. B. Rawls & V. Ch. Ancona, Am. Heart J., February, 1951, 41: 311.—(G. C. Leiner)*

Sudden Death in Asthmatics.—Several of 13 cases of sudden death due to bronchial asthma occurred in patients less than 40 years of age. Heavy sedation with morphine, demerol, or barbiturates appeared the precipitating factor in 9 of these deaths. Autopsy findings were characteristic, with widespread bronchial obstruction due to mucous plugging. Five constant pathologic features were voluminous lungs, mucous plugging, prominent hyalinized basement membranes, emphysema, and eosinophilic infiltration of the bronchial walls. The cause of death is undoubtedly asphyxia caused by widespread bronchial obstruction and emphasizes the dangers of some sedatives.—*Sudden death from asthma, C. H. A. Walton, D. W. Penner, & J. C. Wilt, Canad. M. A. J., February, 1951, 64: 95.—(E. A. Riley)*

Isopropylarterenol for Asthma.—Isopropylarterenol (norisodrine, isuprel, aleudrine, et cetera) has been shown to be a very powerful bronchodilator. Clinical experience has corroborated its value in the treatment of bronchial asthma when used orally, sublingually, subcutaneously, or by inhalation of a nebulized mist. Of 74 patients with asthma and one with allergic cough treated with 25 per cent norisodrine dust by aerohalor, excellent results were obtained in 47 (63 per cent), good to fair results in 14, and poor results in 14. Side effects were mild and transitory and were chiefly similar to those seen with epinephrine. In the large majority of cases, no diminution in therapeutic effect was noted with continued use.—*Norisodrine by aerohalor in asthma, R. E. Kaufman & L. Farmer, Ann. Allergy, January-February, 1951, 9: 89.—(L. Hyde)*

Solid Aerosols.—Aerosols composed of finely divided solid particles of aminophylline, diphenhydramine, and isopropylepinephrine have been evaluated in terms of their ability to prevent the decrease in vital capacity induced in sensitive asthmatic subjects by histamine and methacholine. In each case the solid aerosol yielded results comparable to liquid aerosols; aminophylline was ineffective against either bronchospastic agent, diphenhydramine was an excellent antihistaminic, and isopropylepinephrine protected against both histamine and methacholine. The topical anesthesia following diphenhydramine dust and the cardiovascular stimulation following isopropylepinephrine dust rendered them less valuable for the control of bronchospasm than their liquid aerosol counterparts. Similar solid aerosols of penicillin and streptomycin were assayed in terms of blood levels and urinary excretion. Again results similar to those which followed the administration of liquid aerosols were obtained. These dusts are easier to administer but more likely to produce sensitivity reactions than are liquid aerosols of the same agents (Author's summary).—*Evaluation of solid ("dust") aerosols as therapeutic agents, M. S. Segal, H. J. Rubitsky, E. Bresnick, & L. Levinson, Ann. Allergy, January-February, 1951, 9: 53.—(L. Hyde)*

Analgetic Effect of Nu-2206.—To evaluate 3-hydroxy-n-methyl morphinan (Nu-2206), a synthetic compound resembling morphine

chemically, and to compare it with demerol and morphine, 28 patients were given Nu-2206, 5 mg.; 17 received demerol, 75 to 100 mg.; and 12 received dilaudid, 2 mg. The results with demerol were disappointing. In general, dilaudid was superior, producing moderate to complete analgesia for three to three and one-half hours and permitting routine "stir-up" exercises to be accomplished with ease. Nu-2206 gave analgesia for seven hours; all but 2 patients became euphoric. Respiratory depression was produced if no pain was present. Demerol should not be employed alone for analgesia in thoracic lesions; Nu-2206 has a real place for the control of pain. It is marketed as Dromoran and is subject to the usual federal regulations for narcotics.—*Effectiveness of Dromoran (3-hydroxy-n-methyl morphinan) as an analgesic in thoracic surgery, A. R. Curreri, J. W. Gale, & H. A. Dickie, J. Thoracic Surg., July, 1950, 20: 90.*—(*R. E. MacQuigg*)

Double-Lumen Catheter.—A flexible double-lumen catheter for bronchospirometry was devised with a small rubber hook to engage the carina and inflatable cuffs. The rubber hook is tied down to the catheter during insertion through the glottis; the slipknot is released after passing the larynx. This catheter has been used for bronchospirometry in more than 100 cases with satisfactory results. It has been applied also in 20 pulmonary resections to prevent spillage of secretions during operation. It is the only method that can be applied in cases with suppurative disease in the right upper lobe.—*The prevention of spread during pulmonary resection by the use of a double-lumen catheter, V. O. Bjork & E. Carlens, J. Thoracic Surg., July, 1950, 20: 151.*—(*R. E. MacQuigg*)

Angiography of Pulmonary Carcinoma.—Twenty-six patients with primary bronchial carcinoma and 35 with pneumonia were studied by pulmonary arteriography. Decreased vascularity of the parenchyma was found in 92 per cent of the carcinoma cases, while the pneumonic lung segments showed either normal vascularity or, in 26 of the 35 cases, relative increase in vascularity as compared with the opposite lung. No case of pneumonia showed decreased vascularity of the involved portion of the lung. Pulmonary arteriography is recommended for differentiation of unresolved pneumonia and bronchial carcinoma.—*The differential diagnosis of unresolved pneumonia and bronchiogenic carcinoma by pulmonary angiography, P. G. Keil & D. J. Schissel, J. Thoracic Surg., July, 1950, 20: 62.*—(*R. E. MacQuigg*)

Direct Aortogrpahy of Coarctation.—The surgeon should know as much as possible about the exact nature and location of a coarctation of the aorta. Contrast visualization in which the catheter is inserted into the left radial artery so that the tip of the catheter enters the descending rather than the ascending aorta allows the opaque material to be placed at the point of coarctation. Only 25 cc. of 70 per cent Diodrast is used. Thirteen patients with coarctation were subjected to the procedure. In a 10-year-old boy a dissecting aneurysm was present at operation in the segment immediately distal to the point of coarctation but could not be seen in the aortogram. No internal trauma was found in the specimen but, since the aneurysm appeared recent, it was assumed to be related to the catheterization. This method is recommended because it is technically simple and causes minimal discomfort. No general anesthetic is required except in uncooperative children. There is no danger of the catheter entering a coronary artery. On three occasions the tip passed through the coarctation. There were no untoward reactions except for mild fevers eliminated by proper cleansing of the catheters.—*Experiences with the use of direct aortography in the diagnosis of coarctation of the aorta, W. H. Muller, Jr. & R. H. Sloan, J. Thoracic Surg., July, 1950, 20: 136.*—(*R. E. MacQuigg*)

Tumor Diagnosis by Angiography.—In a case of pulmonary neoplasm the lesion could not be demonstrated by any means other than angiocardiography, partly because it was contiguous to the mediastinum. Pneumonec-

tomy confirmed the type and location of the tumor.—*Contrast visualisation of the pulmonary vessels as an aid in the early diagnosis of pulmonary neoplasms, R. A. Nabatoff, Ann. Surg., February, 1951, 133: 270.*—(*W. H. Oatway, Jr.*)

Ventilation with One Phrenic Nerve.—Maintenance of normal arterial oxygen with electrophrenic stimulation of one phrenic nerve led to the assumption either that the blood vessels of the contralateral lung were constricted, shunting the blood through the aerated lung, or that the contralateral lung was also being aerated. Bronchospirometric observations on 7 subjects revealed that ventilation of the contralateral lung occurred. Roentgenograms show this to be caused by shift of the mediastinum to the stimulated side, followed by expansion of the contralateral lung as well as slight elevation of the unstimulated side of the diaphragm. These data suggest that the therapeutic benefit from phrenic nerve interruption results primarily from partial parenchymal collapse rather than from decreased ventilation or rest in the strict sense.—*Electrophrenic respiration: IV. The effectiveness of contralateral ventilation during activity of one phrenic nerve, S. Sarnoff E. Gaensler, & J. Maloney, J. Thoracic Surg., June, 1950, 19: 929.*—(*R. E. MacQuigg*)

Lymphangitic Carcinomatosis.—The clinical manifestations of lymphangitic carcinomatosis of the lungs often present a difficult diagnostic problem. Symptoms referable to the primary neoplasm are frequently absent or are masked by the pulmonary symptoms. The most striking and constant finding is severe, progressive, and unrelenting dyspnea; cough occurs in approximately 60 per cent and is usually productive of small amounts of white tenacious sputum occasionally tinged with blood. There may be chest pain of the pleuritic type, cyanosis, low-grade fever, weight loss, anorexia, and weakness. Physical examination of the lungs discloses relatively few signs, usually medium rales or occasionally sibilant rales without signs of consolidation. Lymphangitic carcinomatosis of the lungs more often occurs in the younger age group. Chest roentgenograms often are diagnostic, showing thin, stringy, interweaving lines branching out from the hilum. Among 6 cases, lymphangitic carcinomatosis of the lungs was secondary to gastric carcinoma in 3, to rectal and pulmonary carcinoma in one each; the primary site was not found in one case.—*Lymphangitic carcinomatosis of the lungs: Six case reports and a review of the literature, T. E. Hauser & A. Steer, Ann. Int. Med., April, 1951, 34: 881.*—(*T. H. Noehren*)

Streptokinase-Streptodornase for Hemothorax.—Streptokinase will be maximally active if 200,000 to 300,000 units are diluted in 50 cc. of saline or injected into an area which has enough free fluid to dilute out the inhibitor. Two and possibly three types of inhibition of the fibrinolytic system are present in normal serum and in sanguineous exudates: (*1*) Trypsin inhibitor and antifibrinolysin may be the same. (*2*) A specific antibody appears after repeated injections of streptokinase but has been overcome by increasing the dosage. Fibrinolytic activity should persist for periods up to twenty-four hours after an intrapleural injection of streptokinase for hemothorax. Hence, the injected material is left *in situ* for twelve to twenty-four hours; as much fluid as possible then is removed by multiple thoracenteses so that the lysed fluid cannot form a new clot and loculate. A febrile response, occurring in 60 to 70 per cent of the patients, begins six hours after the injection, reaches its peak (averaging 3° F.) in twenty-four hours, and subsides during the ensuing twenty-four to forty-eight hours unless controlled with amidopyrine. Instillation of the enzyme should begin early following the initial gross hemorrhage but after bleeding has ceased. Since lytic action depends on direct contact with the enzyme, multiple simultaneous injections may be advisable. Twenty-seven patients were so treated for various types of hemothorax with highly favorable results.—*The use of Streptokinase-Streptodornase in the*

treatment of hemothorax, S. Sherry, W. S. Tillett, & C. T. Read, J. Thoracic Surg., September, 1950, 20: 393.—(R. E. MacQuigg)

Management of Empyema after Pneumonectomy.—In one-third of the 19 patients with empyema after pneumonectomy, there was no demonstrable leak from the bronchial stump. In each of the 13 patients in whom a leak was present, the fistula healed after rib resection and open drainage. Antibiotics were instilled into the cavity, first through the drainage tube and then through the chest wall for a week after removal of the tube. In no case has fever or increased fluid in the pleural cavity on fluoroscopy been observed at this point. One of the 13 patients required a thoracoplasty and one has a thoracostomy tube after recurrence of the empyema. Two others had recurrence of empyema but were cured by a second course of therapy. Of the 6 patients who developed empyema without evidence of bronchial leak, all but one proved to have a pure infection. The same treatment was pursued except that it was unnecessary to await closure of a bronchial fistula after drainage of the empyema. All responded well but one patient had 2 recurrences requiring final control by thoracoplasty.—*Conservative management of empyema following total pneumonectomy, E. M. Kent, J. Thoracic Surg., September, 1950, 20: 374.—(R. E. MacQuigg)*

Pneumonectomy in Childhood.—Ten of 22 children who had had pneumonectomy at Barnes Hospital were studied. All but one patient with residual disease were leading normal lives. No apparent correlation was found between the age at operation and the physiologic performance. A large residual air volume with reduced ventilatory ability was found in half of the subjects. All of them could perform moderate exercise for seven minutes without a fall in arterial oxygen saturation. Considerable herniation of the remaining lung into the opposite hemithorax was associated with low residual air values, excellent vital capacity and maximal breathing capacity if the mobility of the diaphragm and mediastinum was maintained. The best performance on all tests was found in the 2 most active patients, a gymnast and a construction worker, each of whom had made a concerted effort to overcome his handicap. This suggests the importance of physical training after pneumonectomy and the maintenance of the maximum mobility of diaphragm and mediastinum.—*Respiratory and circulatory studies after pneumonectomy in childhood, R. M. Peters, A. Roos, H. Black, T. H. Buford, & E. A. Graham, J. Thoracic Surg., September, 1950, 20: 484.—(R. E. MacQuigg)*

One-Stage Drainage of Lung Abscess.—After eliminating 46 patients who could not be followed for five years and 4 operative deaths, 115 cases were collected in which acute putrid pulmonary abscess had been treated by one-stage drainage. No patient was considered well until roentgenograms showed complete disappearance of infiltration. Only 3 patients developed hemoptysis shortly after operation; three did not begin to bleed until some years later. Among 154 cases of acute putrid pulmonary abscess operated upon before penicillin was available, 41 were "hyperacute"; 3 of the 4 operative deaths occurred in this group, a mortality rate of 7.3 per cent. All of the 41 patients were so ill that a rapidly performed emergency drainage under local anesthesia was the only operation indicated. There have been no reports of pulmonary resection combined with antibiotic therapy in a substantial number of "hyperacute" abscesses; results in less severe cases appear excellent. When intensive antibiotic therapy does not result in prompt defervescence, reduction of sputum, and diminution of toxicity, one-stage drainage of a fulminating putrid lung abscess appears to be the safest approach; it is followed by resection at a later date if cavitation or bronchiectasis persists. In cases where antibiotic therapy promptly controls infection, primary resection appears the method of choice.—*Acute putrid abscess of the lung: IV. The late results of surgical treatment, A. S. Touroff, R. A. Nabataff, & H. Neuhof, J. Thoracic*

Surg., August, 1950, 20: 266.—(*R. E. MacQuigg*)

Unilateral Cough Reflex Loss after Lung Denervation.—A 40-year-old woman with asthma for sixteen years was treated by isolating the vagus below the recurrent laryngeal nerve and resecting all communicating branches to the root of the right lung. The vagus was transplanted into the pleural cavity and the right sympathetic chain was resected from above the third to below the seventh thoracic ganglia. Postoperatively, there was tenacious secretion and basal atelectasis; at bronchoscopy it was found that the right bronchial tree was insensitive. Severe asthma recurred, and approximately two months after the first operation vagal stripping only was done on the left. Bronchoscopy showed that the left bronchial tree remained sensitive after this procedure. The patient is prey to atelectasis and pneumonitis on the right and it is doubtful if return of function will occur. In the future it is intended to limit denervation to the vagal side of the autonomic arc in view of the untoward complication in this patient.—*Unilateral loss of cough reflex following complete autonomic denervation of the lung for bronchial asthma, S. Levine & J. B. Grow, J. Thoracic Surg., July, 1950, 20: 121.*—(*R. E. MacQuigg*)

Surgery for Pulmonary Coccidioidomycosis.—The results in 30 cases of pulmonary coccidioidomycosis indicate that surgery is effective in arresting the disease and does not cause dissemination to the skeletal or nervous system. Surgery is definitely indicated for giant cavities and for secondarily infected or blocked cavities; for cavity rupture with pneumothorax or empyema; for nonexpansile lung; for continued or severe hemoptysis; and for coccidioma, an expanding lesion. The combination of pulmonary cavities due to tuberculosis and coccidiodomycosis does not constitute a contraindication to surgical management. Surgical treatment in selected cases of pulmonary coccidioidomycosis results in rapid rehabilitation of the patient. Although operation in extrapulmonic infections usually has resulted in further spread, the progressive deterioration of certain patients under medical management left pulmonary resection as the only means of arresting the disease. The results, including a decortication for active coccidioidal empyema healing by primary intention, have led to the conclusion that suitability for operation could be determined without regard to the etiologic nature of the condition or whether the disease was in the dormant or active phase. —*Surgical treatment in pulmonary coccidioidomycosis, B. H. Cotton & J. W. Birsner, J. Thoracic Surg., September, 1950, 20: 420.*—(*R. E. MacQuigg*)

Genesis of Pleural Mesothelioma.—There are still those who dispute the pleural origin of pleural mesotheliomas, believing they are not primary tumors of the lining cells but represent metastatic lesions. The reason for the controversy is that histologic examination alone does not often reveal the potentialities of cells. Lewis has shown by tissue culture that the mesothelium lining the serous cavities is not highly differentiated and may assume different forms. It is not surprising that tumors of the pleural mesothelium assume many of these variations or retain one form only. The particular patterns of 2 types of tumors are not found in metastatic carcinoma: the diffuse, rapidly spreading kind which has both a fibrosarcomatous appearance and, usually, epithelial-like cells; and the localized, fibrosarcomatous, slowly growing tumor in which the epithelial-like element is never present. In one case only the spindle form of cell was apparent until tissue culture was done when the epithelial-like form was demonstrated as well. When tissue culture is used as a diagnostic aid in atypical tumors, it is always advisable to use autogenous plasma in addition to the standard chicken plasma. Actual and potential forms of tumor can not infrequently be demonstrated.—*Pleural mesothelioma, M. E. Sano, E. Weiss, & E. S. Gault, J. Thoracic Surg., May, 1950 19: 783.*—(*R. E. MacQuigg*)

Bronchogenic Carcinoma.—Among 100 consecutive cases of microscopically proved bronchogenic carcinoma in a naval hospital, 70 per cent of the patients, all men, were in the sixth decade. The tumor arose from upper lobe bronchi in 57 per cent of the cases. Of the carcinomas, 54 per cent were squamous, 32 per cent were small-cell or indifferentiated, and 14 per cent were adenocarcinomas. Little correlation between cell type and prognosis could be established. The most frequent site of metastases established by the autopsy examination of 46 patients was the mediastinum, followed in order by lymph nodes other than mediastinal, adrenal glands, abdominal viscera, kidneys, heart, and great vessels. Other sites of metastases were pancreas, esophagus, brain, mesentery, opposite lung, skin, diaphragm, and pleura. Cough, chest pain, blood-streaking, and weight loss were the most common presenting complaints. The admission diagnosis was unrelated to pulmonary disease in 24 per cent of the patients. Although most of the patients were admitted within four months after the onset of symptoms, many were admitted ten months or more after symptoms had appeared. The prognosis was poorest in the latter group. In only 37 per cent of this series was a positive diagnosis established by bronchoscopic examination and biopsy. Of the 71 patients seen in surgical consultation, 37 were judged inoperable; 34 patients underwent surgical exploration; and in 16 the lesion was found unresectable. Resection was performed on the remaining 18 patients; a pneumonectomy on 14, and a lobectomy for "coin"-type peripheral lesions with no gross evidence of mediastinal or hilar node involvement on 4. Of the inoperable patients, 14 received palliative roentgen therapy with considerable temporary benefit in most instances; 4 were given nitrogen mustard with improvement in only one. Among the 18 patients with resections, 4 had palliative procedures only. Of the 14 patients resected with hope of cure, 4 were dead, 2 were alive with known recurrences, and 8 were alive without demonstrable recurrences at the time this study was completed. The longest survival period was twenty-two months. The mortality rate in the 34 patients operated upon was 5 per cent. The operative mortality for the 18 resected cases was approximately the same.—*Bronchogenic carcinoma: A study of 100 microscopically proved cases, R. B. Brown, L. R. Riddle, & M. B. Sullivan, U. S. Armed Forces M. J., March, 1951, 2: 415*—(*E. A. Riley*)

Sputum in Metastatic Pulmonary Malignancy.—Microscopic sputum diagnosis was accurate in 11.8 per cent of 34 cases of metastatic tumors of the lung. The incidence of positive results is low because the surface epithelium remains intact over the metastatic bronchial lesion in many cases. A covering of necrotic tissue in some cases and a protective acellular connective tissue layer in others often prevent recovery of malignant cells.—*Metastatic pulmonary malignancy: A study of factors involved in exfoliation of malignant cells, F. H. Ellis, Jr., L. B. Woolner, & H. W. Schmidt, J. Thoracic Surg., July, 1950, 20: 125.*—(*R. E. MacQuigg*)

Resection of the Carina.—A high percentage of upper lobe tumors are discovered in an inoperable stage because the relatively slight tendency to infection of the upper lobes gives late symptoms. Because of the proximity of the superior vena cava and the ease of involvement of the tracheal wall, a right upper lobe lesion is that most frequently found inoperable. Diodrast outlining of the superior vena cava should be used prior to exploration of any right upper lobe tumor. Dangers previously considered inherent in the "open bronchial stump" are avoided by use of traction sutures to stabilize the mediastinum. With these sutures a defect 9 by 3 cm. in the lateral tracheobronchial wall has been left open for a 32-minute interval without delivering oxygen under positive pressure to the remaining lung and without producing severe anorexia. Six cases are presented. When the longitudinal defect is closed transversely the mediastinum must be maintained slightly to the left of the midline postopera-

tively. Displacement to the right may give local obstruction and may produce pyloric obstruction. The mechanism of this reflex is not understood but the obstruction does not appear to be produced by impulses carried by the vagus nerves.—*Experiences with the surgical resection of the human carina, tracheal wall, and contralateral bronchial wall in cases of right total pneumonectomy, O. Abbot, J. Thoracic Surg., June, 1950, 19: 906.*—(*R. E. MacQuigg*)

Anastomosis of Bronchus.—During the course of a resection of the lingula and left lower lobe for bronchiectasis, the stem bronchus was accidentally divided. An end-to-end anastomosis of the stem bronchus to the upper lobe bronchus was then carried out. Except for a transient atelectasis of the left upper lobe bronchus which was relieved by bronchoscopy, the postoperative course was uneventful.—*End-to-end bronchial anastomosis after accidental division of the stem bronchus, J. Mathey and G. Oustrieres, Thorax, March, 1951, 6: 71.*—(*A. G. Cohen*)

Rupture of the Esophagus.—Fatal spontaneous rupture of the esophagus occurring in a 66-year-old man was complicated by the presence of a tension hydropneumothorax, subcutaneous emphysema, and early mediastinitis. Approximately 60 such cases are recorded in the world's medical literature. It is thought that the rupture is precipitated by a severe bout of vomiting accompanied by failure of the cricopharyngeal muscle to relax followed by a rapid rise of the intraesophageal pressure. The esophagus ruptures at its weakest point, usually on the left posterior wall just above the diaphragm.—*Spontaneous rupture of the esophagus, T. A. Grimson, Brit. M. J., March 17, 1951, No. 4706:568* (*E. A. Riley*)

Pectus Excavatum.—A 28-year-old man with severe funnel chest had incapacitating cardiac symptoms and bilateral bronchiectasis. Detailed pre- and post-operative studies of the circulation showed that the cardiac disability was due solely to impingement on the heart by the involved sternum. The results substantiate the conclusion of Lester and Ravitch that surgical correction of severe or progressing deformities should be accomplished in childhood.—*Pectus excavatum, R. A. Dorner, P. G. Keil, & D. J. Schissel, J. Thoracic Surg., September, 1950, 20: 444.*—(*R. E. MacQuigg*)

Traumatic Rupture of the Lower Trachea.—Traumatic rupture of the lower trachea may occur as a result of a severe chest injury or indirectly because of a sudden tracheal strain. Evidence of such an injury will be manifested by sudden shock, dyspnea, interstitial emphysema over the neck and chest, and the expectoration of blood. Localization of the site of injury in the respiratory tree may be difficult because of pneumothorax and other complicating injuries. Severe tracheal obstruction itself may not occur for some time after the accident. Tracheal obstruction will become apparent when the clinical and radiologic findings show a symmetrical disturbance of the mechanics of the chest. This will be evidenced by bilateral indrawing in the intercostal spaces and bilateral obstructive emphysema. Bronchoscopic examination should be made early to determine the site of the injury. This will be followed in most instances by a low tracheotomy and the use of suitable tubes to maintain an airway. Stenosis may be kept in check by the use of as large a tracheotomy as possible, bronchoscopic dilatations, and the passage of tracheal dilators through the tracheotomy wound. Where the loss of tracheal rings occurs, the treatment is still obscure. Since it would appear that the remaining fibrous channel is unlikely to form a safe airway, new experimental techniques will be required to offer a reasonable chance in such an injury (Author's summary).—*Traumatic rupture of the lower trachea with stenosis, G. A. Henry, Canad. M. J., February, 1951, 64: 134.*—(*E. A. Riley*)

ANTIMICROBIAL THERAPY

Tuberculous Meningitis Survivors.—The survivors among 54 patients treated with streptomycin for tuberculous meningitis be-

tween July 1947 and May 1948 have been followed for two and a half to three and a half years. There are 16 survivors (30 per cent of the group), 3 having relapsed and then recovered after further treatment. No precipitating cause for relapse was found. Patients with miliary tuberculosis complicating meningitis were apparently not more liable to relapse. Sequelae shown by the survivors are deafness in 2 children, minimal hemiplegia in one, retarded development in one, and an intellectual defect in one. Audiometric and vestibular tests done on 14 of the survivors showed complete loss of vestibular response during caloric tests without clinical ataxia when the patients were in a good light. Two patients showed hearing loss. Later manifestations of nonmeningeal tuberculosis have developed in 2 recovered cases. Slight variations of the cerebrospinal fluid findings have been noted but their significance cannot be determined without a further period of observation.—*Tuberculous meningitis treated with streptomycin: Follow-up of survivors for a minimum of two and a half years, W. L. Calnan, J. Rubie, & A. F. Mohun, Brit. M. J., April 14, 1951, No. 4710:794.*—(*E. A. Riley*)

Streptomycin with Thoracoplasty.—Streptomycin in doses of 1.0 gm. daily was given to 325 patients for two days before, and twenty-one days after, each stage of thoracoplasty. The results were compared with 297 control cases in which the drug was used only in the event of a postoperative complication. There was a significantly greater incidence of homolateral spread and serious wound infection in the control group. The incidence of contralateral spreads and the results of sputum examinations performed three months after operation did not differ greatly between the two groups. The routine use of streptomycin prophylactically in thoracoplasty operations is not advocated.—*Prophylactic streptomycin in thoracoplasty operations: Report to the Medical Research Council, Thorax, March, 1951, 6: 17.*—(*A. G. Cohen*)

Streptomycin and Vestibular Function.—The effect of streptomycin on vestibular function was studied in 76 patients with pulmonary tuberculosis treated for twelve to thirty-two weeks. Streptomycin, 2 gm. daily in 0.5 gm. doses, was given to 23 patients. Thirteen received 1 gm. daily in 250 mg. doses and 19 received 1 gm. daily in a single injection. Another 4 patients received 2 gm. daily in 0.5 gm. doses during alternate weeks, and 6 patients were given the same dosage during alternate months. A group of 11 patients was treated with streptomycin, 1 gm. daily in a single injection, with *p*-aminosalicylic acid (PAS), 5 to 20 gm. daily. Giddiness, occasionally preceded by misty vision or difficulty in reading was noted by 14 (60 per cent) of the patients receiving streptomycin, 2 gm. daily, but only by 7 (10 per cent) of those receiving 1 gm. daily. The incidence of giddiness was higher among those patients receiving streptomycin on a divided dosage regimen than among those receiving one daily injection. This difference may be related to the differing purities of the batches of streptomycin employed. Giddiness developed later among the group of patients receiving streptomycin, 1 gm., than among those receiving 2 gm. daily. In only 2 patients, both on the latter regimen, giddiness was disabling. Nystagmus on lateral gaze was observed in 63 per cent of the patients on streptomycin, 2 gm. daily, and in only 16 per cent of those receiving 1 gm. daily. It was present in 75 per cent of the patients complaining of giddiness as compared with about 15 per cent of those who did not. Among 13 patients with normal caloric reactions prior to streptomycin therapy and studied during the fourth month after they received streptomycin, 2 gm. daily, 8 had reduced or absent caloric reactions. Three of these patients showed no evidence of recovery on re-examination twelve or more months after cessation of streptomycin therapy. Although alteration of caloric function was commonly associated with giddiness, the caloric response was sometimes abolished without symptoms of vestibular damage. Among 6 patients, 5 of whom had lost the caloric reaction, ataxia was so marked that walking with the eyes closed became impossible. With larger doses of streptomycin,

nearly two-thirds of the patients developed nausea with giddiness at some time. The use of antihistaminic drugs abolished nausea but had no effect upon giddiness. Some evidence suggested that antihistiminic drugs might have some prophylactic value in preventing vestibular dysfunction. The retention of a normal galvanic response after the caloric response had disappeared strongly suggests that the site of the toxic action of streptomycin is upon the labyrinth.—*Effect of streptomycin on vestibular function, J. R. Bignall, J. W. Crofton, & J. A. B. Thomas. Brit. M. J., March 17, 1951, No. 4706:554.*—(*E. A. Riley*)

Alkaline Streptomycin for Tuberculous Empyema.—Streptomycin has been relatively ineffective in controlling tuberculous empyema because the agent is inhibited by an acid medium such as is found in tuberculous empyema. If the empyema gets worse, the pH falls; and with improvement it tends to rise. Furthermore, bronchopleural fistulas may be helped to heal only by early parenteral streptomycin when they are fresh, soft, and small. The authors treat tuberculous empyema by inserting a long trocar through the first or second interspace at the mid-clavicular level with the patient in dorsal decubitus and the lower part of the body slightly elevated. The pus can be totally evacuated but the trocar tract is not bathed in pus afterward and chances of fistulization are diminished. When the pleural cavity is empty, it is washed with physiological saline solution until the fluid is clear. Then 0.5 to 1 gm. of streptomycin in 15 cc. of 25 per cent sodium citrate is injected. If there is a mixed infection, 100,000 to 200,000 units of penicillin are added. To promote healing of fresh bronchopleural fistulas, 0.5 gm. of parenteral streptomycin is given every twenty-four hours. Collapse therapy is maintained until the empyema improves or disappears and then is maintained or discontinued according to the status of the pulmonary lesion. Of 35 patients with frank pus containing tubercle bacilli, 15 had bronchial fistulas; 23 were cured, with disappearance of fluid, sterilization of the pleural cavity, and closure of the bronchial fistula. Another 10 were improved.—*Streptomycin plus alkalinization of the pleural cavity in the treatment of tuberculous empyema, E. Staines & C. Cardenas, J. Thoracic Surg., June, 1950, 19: 891.*—(*R. E. MacQuigg*)

Pulmonary Tuberculosis and Thiosemicarbazones.—A series of 25 patients with moderately and far advanced pulmonary tuberculosis were treated for three months with 4-acetylaminobenzal-thiosemicarbazone (amithiozone), 200 mg. daily. A total of 8 patients were unable to complete the course because of severe toxic symptoms in 4, roentgenographic evidence of extension in 2, and severe neutropenia in 2. Progressive anemia with blood and marrow findings suggesting a maturation defect developed in 5 patients. Anorexia, nausea, and vomiting were severe. The therapeutic results in the patients completing the course were equivocal. Roentgenographic examination at the end of the study showed improvement in 10 patients. This was compatible with the effect of bed rest alone and was comparable with results noted with *p*-aminosalicylic acid. No roentgenographic change was noted in 8 patients and extension of the disease developed in 7. The disadvantages of this therapy far outweigh any possible benefits, and toxicity of the drug precludes its use even as an adjunct to streptomycin.—*The treatment of pulmonary tuberculosis with the thiosemicarbazones, J. J. Shane, C. Riley, J. H. Laurie, & M. Boutilier, Canad. M. A. J., April, 1951, 64: 289.*—(*E. A. Riley*)

Intrathecal Sulphetrone.—Of 48 patients treated for tuberculous meningitis between May, 1948 and November, 1948, all except 3 were less than 15 years of age. In 47, the diagnosis was proved bacteriologically. In addition to intrathecal and intramuscular streptomycin, half of the group were given Sulphetrone, 200 mg. intrathecally, mixed with the daily dose of streptomycin. Toxic reactions consisting of convulsions, excessive head retraction, opisthotonos, mental symp-

toms, and cyanosis were encountered in 16 patients and necessitated cessation of treatment in 5 of the 24 patients so treated. The daily dose of streptomycin was 0.02 gm. per pound of body weight in twenty-four hours intramuscularly, and 0.1 gm. in 10 ml. of normal saline intrathecally. All patients were observed for a minimum period of twelve months from the start of treatment. The survival rate in the 2 groups was the same and, in addition to the survival rate, no appreciable clinical difference was found between the 2 groups. Among the 48 patients only 3, none of whom received intrathecal Sulphetrone, developed bacterial resistance to streptomycin to a significant degree.—*Tuberculous meningitis: Result of treatment with streptomycin and intrathecal Sulphetrone, W. L. Calnan, J. Rubie, & A. F. Mohun, Brit. M. J., April 14, 1951, No. 4710:792.—(E. A. Riley)*

Oral Penicillin for Pneumonia.—Because of the disadvantages of repeated parenteral therapy, the efficiency of a modified oral therapy with penicillin was investigated. To ensure the rapid achievement and maintenance of an adequate blood level of the drug, a single initial intramuscular injection of penicillin was given and *p*-(di-n-propylsulfamyl)-benzoic acid (Benemid), a drug decreasing the renal excretion of penicillin, was administered throughout the course of treatment. Two comparable groups of patients with pneumococcal lobar pneumonia were studied; 43 received one injection of aqueous penicillin G intramuscularly at the start, together with Benemid, 1 gm., by mouth. At the next 8 o'clock treatment period and every twelve hours thereafter, 300,000 units of penicillin G were given by mouth with Benemid, 1 gm. Treatment was continued until the rectal temperature was below 99.6°F. for seventy-two hours. The other group of 57 patients received 300,000 units intramuscularly without Benemid on the same schedule. There was no significant difference in the results obtained in the two groups.—*The efficacy of modified oral penicillin therapy of pneumococcal pneumonia, R. Austrian, G. S. Mirick, D. E. Rogers, S. M. Sessoms, P. A. Tumulty, W. H. Vickers, Jr., & C. G. Zubrod, Bull., Johns Hopkins Hosp., March, 1951, 88: 264.—(J. S. Woolley)*

Oral Aluminum Penicillin for Pneumonia.—Oral aluminum penicillin, 300,000 units, with 1.8 gm. of sodium benzoate was given every twelve hours to 37 patients with pneumococcal pneumonia. The results were satisfactory, comparing favorably with patients receiving aqueous penicillin intramuscularly. To avoid the possible hazard of delayed penicillin absorption by severely sick patients, it is recommended that an initial parenteral injection of penicillin precede the oral regimen. —*The treatment of pneumococcal lobar pneumonia with oral aluminum penicillin, J. C. Harvey & G. S. Mirick, Bull., Johns Hopkins Hosp., March, 1951, 88: 270.—(J. S. Woolley)*

LABORATORY STUDIES

Alveolar Ventilation.—Certain types of pulmonary abnormalities may be detected with a new clinical test. By continuous measurement of the nitrogen concentration and volume flow of alveolar gas expired after a single breath of oxygen, it is possible to detect uneven distribution of inspired gas in the lungs. The test does not diagnose specific types of pulmonary disease but directs attention to a definite abnormality which can be explored more fully by other methods. A comparison has been made in 77 patients of this new test with the seven-minute pulmonary nitrogen emptying rate of Cournand and associates. The single breath analysis revealed abnormal distribution in 77 per cent, whereas the seven-minute test was abnormal in only 32 per cent. The test is rapid, objective, and requires only a minimum of cooperation on the part of the patient (Authors' summary). —*Lung function studies: VI. Detection of uneven alveolar ventilation during a single breath of oxygen, J. H. Comroe, Jr. & W. S. Fowler, Am. J. Med., April, 1951, 10: 408.—(T. H. Noehren)*

Artificial Intima for Perfusion Apparatus.—In perfusion apparatus, the blood passes through glass and rubber tubes which are not as smooth as the intima of blood vessels. Perfusion for some hours will cause slight hemolysis, fibrin formation, and foaming. The fibrin formation and foaming can be avoided by heavy doses of heparin but this heparin has been difficult to neutralize with protamine, resulting in considerable risk of hemorrhage after intrathoracic operations. Paraffin, polyvinylchloride, and organosilicon polymeric compounds were used as water-repellent coatings. To coat tubes directly with silicones, Siloxan UHB 300 was poured through the equipment which was then autoclaved for an hour and rinsed with sterile saline. A relatively small heparin dose could then be used.—*An artificial intima for perfusion apparatuses, V. O. Bjork, J. Thoracic Surg., September, 1950, 20: 474.*—(*R. E. MacQuigg*)

PUBLIC HEALTH AND EPIDEMIOLOGY

Tuberculous Infection.—The object of the study was to determine the effects of subclinical tuberculosis upon the health of children. The heights and weights of 4,000 school children were determined. No significant difference was noted between tuberculin positive and -negative children.—*Investigation into the effects of tuberculous infection on the physical growth of children, B. Benjamin & F. A. Nash, Tubercle, April, 1951, 32: 82.*—(*A. G. Cohen*)

Carcinoma of the Lung.—In the mass chest roentgenographic survey conducted in Boston, 536,012 miniature films were taken. On the basis of larger follow-up films, 398 persons were finally determined to be cancer suspects. A complete work-up was possible in 343 cases. Based on this, 267 were finally reported not to have cancer. This left 76 cases reported as cancer. Of these, 43 were proved to have primary lung cancer; 20 underwent resection, 21 were inoperable, and 2 refused operation. There were 3 cases of lymphoblastoma and 15 cases of metastatic carcinoma. The remaining 15 were presumed to have cancer but could not be studied further. These cases were studied by a separate panel from the one which reviewed the tuberculosis cases. The panel was assisted by social workers and secretarial help. The cost per patient for the detection of the 76 suspects was $53, which is not considered high.–*Follow-up study of lung cancer suspects in a mass chest X-ray survey, C. L. Scammon, New England J. Med. April 12, 1951, 244: 541.*—(*A. G. Cohen*)

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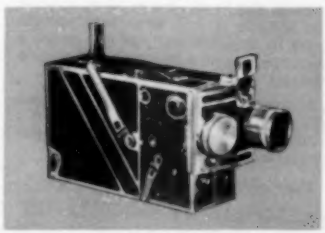

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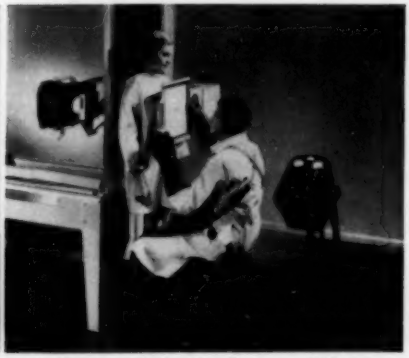

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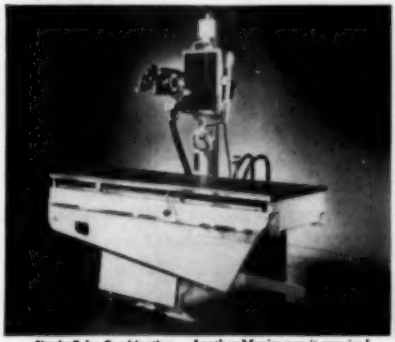

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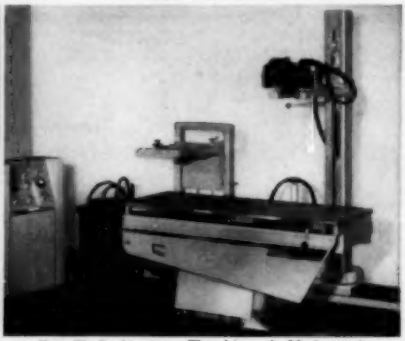

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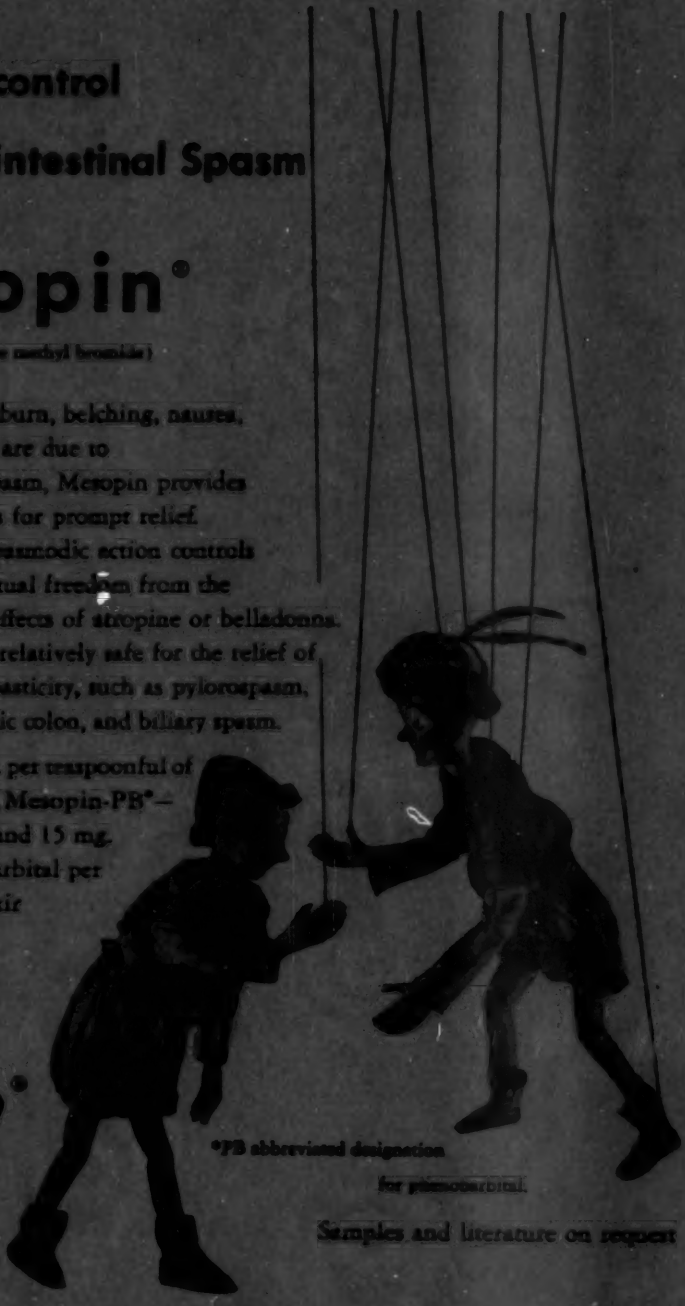

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